THE OPHTHALMOSCOPE

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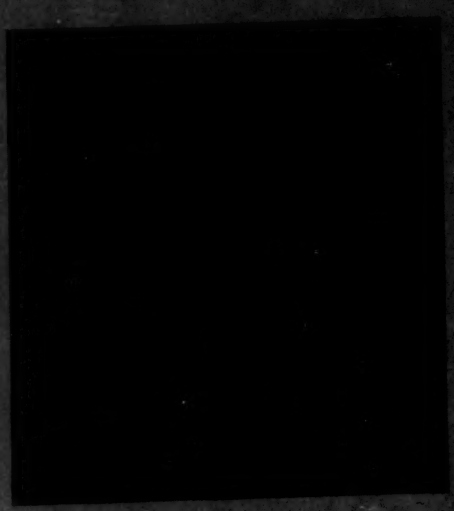

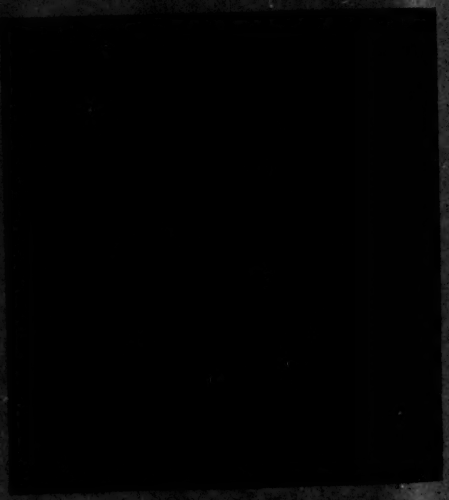

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OPHTHALMOLOGY

FEBRUARY, 1950

COMMUNICATIONS

DEAFNESS AND THE LAURENCE-MOON-BIEDL SYNDROME*

BY

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IN this report two families are described, one showing the syndrome with deafness, the other the syndrome alone. The literature of the subject as a whole is reviewed to complement the last extensive survey of Sorsby, Avery, and Cockayne, which closed in 1937. In addition, all case reports published since 1864 in which deafness is recorded in connection with the syndrome are analysed to determine whether any relation exists between the two.

CASE REPORTS

The H—family.

Attention was drawn to this family when the two sisters with ocular defects attended the Royal Eye Hospital. The parents are first cousins and they have had nine children.

* Received for publication July 13, 1949.

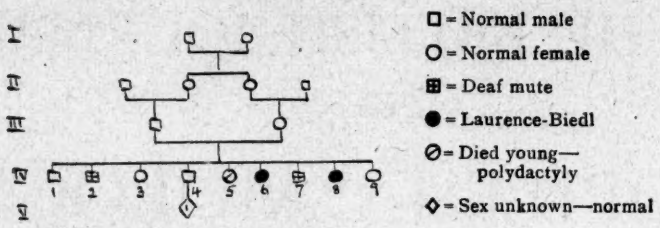

FIG. 1. Pedigree of the H-. family (condensed).

(IV, 1) The first son was not seen. He is an intelligent man who has won scholarships and is a well-qualified musician. The parents say he has no defects. He is 33 years old.

(IV, 2) The second son was examined. He is 32 years old, and a deaf mute. His intelligence is normal and he plays chess. He is married. There is no visual defect and the fundi are normal. There is no polydactyly and *x* ray of the hands and feet shows no abnormality of the bones. He is thin. The ear drums are normal. The deafness is complete and of the nerve type. He has never been able to hear. *X* ray of the skull shows a small sella turcica.

(IV, 3 and 4) The third and fourth children were not seen, but the parents say they have no defects and lead normal lives. The fourth is married and has one child, a few weeks old, which is said to be normal (V, 1).

(IV, 5) The fifth child, a daughter, died of diphtheria at the age of ten months. She is said to have had one extra toe.

(IV, 6) The sixth child, Hilda H—, was examined and shows all the components of the Laurence-Biedl syndrome except hypogenitalism.

History. She was backward and suffered from night blindness in childhood. As a result, she was sent to a blind school, and now works filling flour bags on a machine. Menstruation started at 13 years and was normal. She has lately married.

Examination. Her behaviour is that of a cheerful child. She is plump, not grossly obese, but the fat is unevenly distributed over the proximal parts of the limbs and lower abdomen. There are striae over the hips and abdomen. She was menstruating at the time of examination. Development of breasts and distribution of axillary and pubic hair are normal.

The fingers and toes are short, and there are old scars on the outer borders of the feet where extra toes have been removed. The second and third toes of both feet are webbed. *X* ray showed angulation of the outer border of the right fifth metatarsal, suggesting that a bifid portion had been removed. There was a rough place on the lateral aspect of the left fifth metatarsal, probably for the same reason. The middle phalanges of the index and little fingers of both hands were abnormally short.

Her eyes showed fine rotatory nystagmus. The pupils reacted sluggishly to light. She was only able to count fingers at 3 ft. with or without glasses. The optic discs were atrophic, the arteries grossly attenuated, and there was much pigmentation of the fundus. The pigment was collected in coarse clumps and masses, mostly equatorial in distribution, though there was some finer stippling at the maculae. There was approximately −4D. of myopia in each eye.

There was no abnormality of the other systems on clinical examination. Her speech and hearing were normal. *X* ray of the skull showed no significant abnormality.

(IV, 7) The seventh child, a man, aged 23 years, was examined. He is a deaf mute, and at present a patient in a mental hospital.

History. His hospital record shows that he is emotionally unstable, became violent towards his mother, and has delusions that he is suffering from infantile paralysis.

Examination. He is not as intelligent as his deaf brother, but much of his dullness may be attributed to his psychosis.

There is no obesity and the sexual organs and secondary characteristics are fully developed.

There is no polydactyly or other anomaly of the hands or feet, either clinically or visible on *x* ray.

The pupils react normally to light and accommodation. He is able to read type equivalent approximately to Jaeger 1. There is no abnormality in the fundi.

Wassermann reaction and Kahn test are both negative. *X* ray of the skull shows no abnormality.

He is completely deaf and almost entirely dumb. The deafness is of the nerve type, and the ear drums are normal.

Like his deaf brother, he shows none of the components of the Laurence-Biedl syndrome.

(IV, 8) Elizabeth H—, the eighth child, was examined.

History. She showed night blindness and backwardness in childhood, and was sent to a blind school. She does not work. Menstruation started at the age of 12 and has remained normal.

Examination. There was a marked facial "tic" and her mentality was behind that of her affected sister. The degree and type of obesity was similar to that of Hilda, and the secondary sexual characteristics were similarly developed. The condition of the eyes, including the fundus, was practically the same. *X* ray of the skull showed no significant abnormality, apart from a deep sella turcica. Other systems were normal on clinical examination.

There was no polydactyly or syndactyly but *x* ray showed that the terminal phalanges of the toes were small and fused to the middle phalanges, while the fingers are similar to Hilda's.

She shows, therefore, the same components of the syndrome as her sister, except that her digital anomalies do not include polydactyly or syndactyly.

(IV, 9) The ninth child, a daughter, aged 21 years, was not examined, but was reported to be normal in all respects.

Both parents were examined and showed no abnormality of importance. There was a mosaic of small yellowish spots at both maculae in the mother. This is probably an unrelated senile change and does not impair vision.

Details of the pedigree and antecedents were provided by the parents, who are both intelligent and well-informed on family matters. No significant family abnormality was reported in the antecedents or collaterals, except for a mentally deficient child, a cousin on the father's side. As he was the first-born of his mother at the age of 44, the fact is probably not relevant.

The salient features in this family are therefore :—

(1) The parents are first cousins and they had nine children, of whom five were abnormal.

(2) Two female sibs show the complete syndrome except for hypogenitalism. One female sib died young and was reputed to have had polydactyly.

(3) Two male sibs are deaf mutes but show none of the components of the Laurence-Biedl syndrome.

(4) There is no history of any related abnormality in the parents, ascendants or collaterals.

The B—family.

Details of this family, which have not previously been published, were kindly supplied by Dr. Raymond Greene.

The parents were not related. There were no other sibs.

Diana B—, first seen October 28, 1947, aged 12 years.

History. Her mother complained that she had been overweight since the age of four and that her weight had rapidly increased during the last four years. She was said by a schoolmistress to be three years behind her age intellectually. She

had never menstruated. Apart from measles she had had no illness. A sixth digit had been removed from each foot.

Examination. She was a grossly fat girl with no sign of sexual development. The breasts were prominent, but the prominence was due to fat and no mammary tissue could be palpated. The forearms were hairy. The hair distribution otherwise was normal except for a complete absence of pubic and axillary hair. Height 4 ft. 8½ ins., weight 12 st. 7 lbs. Pulse 80.

The fundi showed the characteristic picture of retinitis pigmentosa with considerable optic atrophy and greatly reduced vision. *X* ray of the skull was normal.

Antony B—, admitted to the Royal Northern Hospital January 3, 1948, aged 16 years.

History. He had been obese since the age of two, was mentally backward, was partially blind and had never developed sexually. He had a mild attack of chorea at the age of 8, severe hemichorea on the right side at the age of 11 and on the left at 12. At 15 he had a further severe bilateral attack.

Examination. He was grossly overweight. The genitalia were extremely small; sparse pubic hair of female distribution was present, but body hair was otherwise absent. There was severe genu valgum. Vision was considerably reduced and there was convergent strabismus. The fundi showed attenuation of the arteries and there were scattered spots of black pigment in the lower periphery of both eyes.

There was no record of any significant abnormality in parents, ascendants or collaterals.

The salient features in this family then are :—

(1) The parents are unrelated and had only two children, both affected.

(2) The girl shows the complete syndrome; in the boy, polydactyly is lacking on clinical examination.

(3) There is no record of abnormality in the ascendants or collaterals.

LITERATURE

The first cases reported as a separate clinical entity were those of Laurence and Moon from the Royal Eye Hospital in 1866. Höring (1864) and Stör (1865) had reported cases of retinitis pigmentosa combined with other anomalies which were probably unrecognized cases of the syndrome. Cockayne, Krestin, and Sorsby (1935) and Sorsby, Avery, and Cockayne (1939) have reviewed the literature up to 1937. The present review deals with the cases recorded since then; and surveys, from the literature as a whole, all the recorded cases in which deaf-mutism has occurred.

THE LITERATURE SINCE 1937

The total number of cases reviewed by Cockayne and others (1935) and Sorsby and others (1939) up to 1937 was 178, distributed in 121 families. The corresponding figures for 1938-48 are 82 and 57, excluding a small number of reports which were unobtainable.

Because of the inconstancy of expression in members of the same sibship cases have been accepted as belonging to the Laurence-Biedl group if they showed three of the five classical

components of the syndrome. Doubtful cases have been included if there were records of other components occurring in relatives; for example, the case of Warkany and Weaver (1940) which had obesity, hypogenitalism, mental deficiency, and unilateral microphthalmos, has been accepted because an uncle was reported to have had polydactyly. A number of doubtful cases, which have been rejected from the analysis, are nevertheless described at the end of this section because they are probably allied to the syndrome.

Ascendants and Collaterals.

Obesity in ascendants is reported by Likins and others (1947), Taylor (1947), Demirag (1944), Ruggeri (1938), Laborne (1944), and Bergouignan and Viaud (1946); polydactyly by Scott and Johnson (1942), Ellis and Law (1941), Lurie and Levy (1942), Wolff (1938), Warkany and Weaver (1940), Muthayya and Iyer, quoted by Kutumbiah and Abbu (1942), and Marmor and Lambert (1938). There are reports of mental defect by Likins and others (1947), Demirag (1944), Kutumbiah and Abbu (1942), and Scott and Johnson (1942); visual defect by Baldi (1945), and Taylor (1947); miscarriages by Taylor (1947); and epilepsy by Schwartz and Boudreau (1940).

The only defects reported in collaterals were retinitis pigmentosa, and retinitis pigmentosa with obesity in second cousins (Laborne, 1944); undiagnosed visual defect in two cousins (Baldi, 1945); and dementia praecox in a cousin (Novick, 1939).

Transmission.

Apparently direct transmission is recorded by Laborne (1944), and by Lurie and Levy (1942).

(i) *Laborne (1944).*

In this case the affected father married a second cousin. Two out of three children were affected. The pedigree shows the occurrence of the partial syndrome in ascendants and collaterals and direct transmission from father to children.

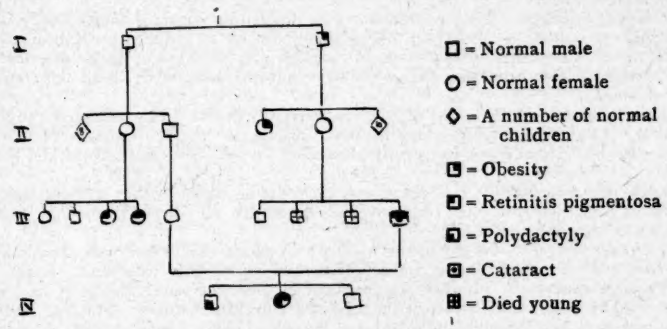

FIG. 2. Pedigree condensed from Laborne (1944).

(ii) *Lurie and Levy (1942).*

In two families one component only, syndactyly, was directly inherited, in the one case from the mother and in the other from the father. In the former case transmission was known to two generations only. In addition a cousin on the mother's side was affected. In the latter there was evidence of transmission through three generations, the patient, father, and a paternal grandfather being affected. These cases are more fully described in the section on deafness. Baldi (1945) reports the birth of an apparently normal child to an affected woman.

Sibs.

The syndrome may vary in its manifestations within the sibship. Polydactyly alone in deceased members is often reported (Borsotti, 1939; Radner, 1940; Ruggeri, 1938; Montanaro and others, 1942; D'Abreu and Ferriman, 1941). But variation is often seen in living affected members. In the family of D'Abreu and Ferriman there were seventeen members. One had adiposo genital dystrophy and a retinal lesion with cataract, another was said to have had polydactyly with normal vision, four more were said to have been blind from birth but there is no record of obesity or polydactyly. The children of the patient reported by Laborne were differently affected. One had polydactyly only, another had polydactyly, obesity and a retinal lesion, the third was normal. Taylor's case (1947) with the complete syndrome was said to have had a sister still-born with polydactyly and "part of the head missing." In Snell's (1942) sibship of eight, one had the complete syndrome, one died young and was reported to have obesity and polydactyly, one other was examined and found to have only the retinal lesion and shortening of the fourth metacarpals with thickening of the skull bones.

Isolated abnormalities as distinct from partial expressions of the syndrome are rare. Mental deficiency is reported in one sib by Ellis and Law (1941). There are other reports suggesting mental defect in otherwise normal sibs (Muthayya and Iyer, quoted by Kutumbiah and Abbu, 1942; Marmor and Lambert, 1938; Novick, 1939). The present report shows two affected children and two deaf mutes in the same sibship.

Components of the Syndrome.

(*a*) *Obesity.* This component was definitely absent in 6 cases only (Roth, 1947; Snell, 1942; Borsotti, 1939; Laborne, 1944). In Roth's cases of four affected sibs two were obese and two not. In Snell's case the other living affected sib was fat and one dead sib was reported to have had polydactyly and obesity. In Borsotti's cases not only obesity but also hypogenitalism and mental defect appear to have been missing in both cases. In Laborne's case one child had polydactyly only, while the other had obesity and retinitis pigmentosa as well. Obesity without hypogenitalism was recorded in four instances (Snell, 1942; Baldi, 1945; Laborne, 1944; Graham Anderson, 1948). Hypogenitalism without obesity was recorded by Roth in two of four affected members of the same sibship.

(*b*) *Hypogenitalism.* This component was much less constant than obesity. It is difficult to assess, especially in young girls, and in 20 cases the diagnosis was doubtful. It was definitely absent in 14 cases (see Appendix A). In Baldi's (1945) case a woman with otherwise the complete syndrome gave birth to an apparently normal child.

(*c*) *Polydactyly.* Anomalies of the extremities varied from complete supernumerary digits to syndactyly and irregularities in the length of the metacarpals. Short "podgy" hands are frequently described, as well as incurving of the little finger.

Polydactyly was absent, and there was no mention of any other definite abnormality of the extremities in 18 cases (see Appendix A), digital anomalies being reported in the relatives of five.

(*d*) *Ocular defects.* In the great majority of cases the defect was retinal and was first noticed in early childhood. The most usual type was some variant of the classical picture of retinitis pigmentosa, the pigment being the least and the optic atrophy and vascular narrowing the most constant features. Macular lesions were reported by Taylor (1947) and by Borsotti (1939). Low myopia is noted in the present study in combination with the retinal lesion. Unilateral microphthalmos was reported in the case of Warkany (1940).

(*e*) *Mental deficiency.* This component was definitely absent in 11 cases (see Appendix A). Either the record or the diagnosis was doubtful in 13 cases.

Pathology.

Reports of two post-mortem examinations have been added to the literature since 1938 (N. L. Anderson, 1941; Radner, 1940).

(i) *N. L. Anderson (1941).*

The reproductive organs were rudimentary, the anterior lobe of the pituitary consisted chiefly of basophil and eosinophil with very few chromophobe cells, there was a colloid goitre, and the brain and its blood vessels were normal.

(ii) *Radner (1940).*

The only point of importance was the finding of uterus duplex.

Race.

Cases have been reported in Indians (Kutumbiah and Abbu, 1942; and Muthayya and Iyer, quoted by Kutumbiah and Abbu, 1942) and in Negroes (Roth, 1947; Snell, 1942; Scott and Johnson, 1942).

Associated conditions.

(*a*) *Ocular.* Nystagmus was recorded by many authors (Taylor, 1947; Roth, 1947; Garcin, Mann, and Piguet, 1945; Beato Forn, 1940; Marques, 1941; Kloess, 1941; Baldi, 1945; Family H—, present report). Strabismus was noted by Bergouignan and Demirag (1944), Montanaro and Turro (1942), Lurie and Levy (1942), and in Family B— of the present report; ptosis by Lurie and Levy (1942), and Krarup (1939).

(*b*) *Skeletal.* Genu valgum and pes planus occurred together in several instances (Garcin, Mann, and Piguet, 1945; Parella, 1938; Marmor and Lambert, 1938; Montanaro and Turro, 1942; Beato Forn, 1940; Kutumbiah and Abbu, 1942). The former, with no mention of the latter was recorded by Taylor (1947), Warkany (1940), Marques (1941), Scott and Johnson (1942), and N. L. Anderson (1941), and in Family B— above. Kyphosis, with or without lordosis, was mentioned by Garcin, Mann, and Piguet (1945), Attiah and El Gamal (1940), and Kutumbiah and Abbu (1942). Dorsal scoliosis is recorded by Taylor (1947). Bowing of one leg with a slipped epiphysis was described by Scott and Johnson (1942). Genu valgum, pes planus, and dislocation of the hip were reported by Jaso and Arbelo (1945) in a case of doubtful diagnosis (see below), the outstanding feature of which was enormous obesity in a boy of 9½ years.

An abnormally high palate was observed by Attiah and El Gamal (1940), and by Scott and Johnson (1942)—in the latter case combined with hypoplasia of the mandible. Warkany and Weaver (1940) reported enlarged parietal openings and overflexible joints. Dwarfism was recorded in one case (Ellis and Law, 1941).

(*c*) *Abnormalities of the central nervous system.* Ataxia and scanning speech were reported by Roth (1947); ataxia, adiadokokinesis, and excessive spontaneous blinking by Garcin, Mann, and Piguet (1945); excessive blinking by Beato Forn (1940); and difficult speech by McCullagh and Ryan (1941). Tremor, deviation of the tongue, and Rombergism were described by Lurie and Levy (1942), and epilepsy is mentioned by Schwartz and Boudreau (1940).

(*d*) *Metabolic disturbances.* Diabetes insipidus was recorded by Lyle (1946), Morgensen (1941), Bernard and Chassagne (1938), Lurie and Levy (1942). No polydipsia or polyuria was recorded by Lyle (1946), Garcin and others (1945), Montanaro and Turro (1942), or Lurie and Levy (1942). Polyphagia was reported by Likins and others (1947), and Lurie and Levy (1942); its absence was noted by Lurie and Levy (1942). The basal metabolic rate was low in most of the cases where it was recorded (see Appendix B). Glucose tolerance was reported normal by Likins and others (1947), Montanaro and Turro (1942), Garcin and others (1945), Krarup (1939), Morgensen (1941), Ruggeri (1938), and Wolff (1938); and as increased by Attiah and El Gamal (1940), Lurie and Levy (1942), and Wendt (1941).

Tetany of unknown cause, with normal blood calcium and phosphorus, was reported by D'Abreu and Ferriman (1941).

(*e*) *Developmental abnormalities.* Atresia ani, in a deceased sib with polydactyly, and uterus duplex are reported by Radner (1940). Hypospadias is mentioned by N. L. Anderson (1941).

Doubtful cases not included.

Two cases, reported by Ciotola (1938), of polydactyly or syndactyly with microphthalmos, occurring in separate non-consanguineous sibships, have not been

included. They were quite free from any other component of the syndrome, except for unilateral undescended testicles in one child aged two, nor is there any record of affected sibs or ascendants.

The family reported by Jaso and Arbelo showed obesity and a retinal condition in which vascular stasis appears to have been the leading feature. There is no mention of any component, other than obesity, in the relatives and the pedigree shows direct transmission of this defect from parents to children in three generations.

Marañon (1941) describes a family of 11 in which two sisters and one brother were affected. The elder sister had hypogenitalism and obesity due to a proved pituitary tumour. Another sister had obesity, hypogenitalism and abnormalities of the hands and feet—gross inequality in length of toes and dwarfing of thumbs. The younger brother was reported, on medical evidence, to be mentally defective and to have a slight degree of oxycephaly and malformation of the ears. Nothing is said about consanguinity. No abnormalities were known in the parents or antecedents.

DEAFNESS IN THE LITERATURE AS A WHOLE

In families affected by the Laurence-Biedl syndrome, deafness occurs both in combination with and independent of the syndrome. In the literature reviewed by Sorsby and his colleagues up to 1937, there are reports of deafness occurring in 7 families and affecting 13 individuals. From 1938-48 there are 6 families and 9 individuals affected, including this record, making a total in the literature of 13 families and 22 individuals.

Deafness in cases of the syndrome.

Nine family groups and thirteen individuals come under this heading.

(i) *Boenheim (1929).* A sibship in which three brothers were affected. The number of normal sibs is not stated. One showed mild obesity and hypogenitalism, retinitis pigmentosa, and partial nerve deafness which appears to have been first noticed between 16 and 17 years old. There was no polydactyly or mental deficiency. Another brother was said to complain of night blindness and to be mentally normal. The third brother had retinitis pigmentosa, hypogenitalism, mental deficiency and impaired hearing. He was thin and had no polydactyly. The parents were not related.

(ii) *Weiss (1932).* Two sisters showing obesity, hypogenitalism, mental deficiency and nerve deafness. There were no ocular defects or polydactyly, but one of the father's relatives was said to have had six fingers. Two other sisters were normal. There is no statement as to consanguinity of the parents.

The deafness in one was only noticed at the age of 6, and she talked normally; in the other it was not discovered till about 10 years old, though she talked with difficulty. It seems probable, despite the late onset, that this was a true nerve deafness of genetic origin, since both sisters were similarly affected.

(iii) *Steinberg (1937).* Family 1. Five siblings of whom the third and fourth were normal, the first and fifth had retinitis pigmentosa and mental defect, and the second had polydactyly in addition. The three affected female sibs were congenital deaf mutes. The parents were first cousins and healthy apart from some nerve deafness in the mother, probably of senile type.

(iv) *Steinberg (1937).* Family 2. A boy suffering from obesity, hypogenitalism, mental deficiency, and retinitis pigmentosa. He had no polydactyly but was a congenital deaf mute. The father and three sisters were healthy. The mother had a degree of acquired deafness but no other abnormality of importance. There is no mention of whether the parents were related or not.

(v) *Becker (1937).* Four siblings, of whom one died young, two sisters were well and one brother had the complete syndrome except for polydactyly. He was also a congenital deaf mute. Nothing is said of consanguinity in the parents or components of the syndrome in ascendants.

(vi) *Attiah and El Gamal (1940).* A boy with the complete syndrome and impaired hearing. The parents were first cousins and there was a history of developmental anomalies and defective vision amongst the grandparents. The siblings were a younger brother who had the syndrome but not deafness, and a male child who died aged 2 years. It is not possible to be certain whether the deafness was of genetic origin or not.

(vii) *Lurie and Levy (1942).* Family 1. A boy with mild obesity and hypogenitalism, mental deficiency, syndactyly, and impaired hearing of nerve type present since early infancy. The eyes were normal. The parents were not related. The father was normal, but the mother had syndactyly of both feet. One maternal uncle and one maternal aunt were blind from early life. One female cousin on the mother's side had syndactyly. There were five other siblings all older and all normal.

(viii) *Lurie and Levy (1942).* Family 2. This was a girl with obesity, hypogenitalism, polydactyly and syndactyly, mental impairment and defective hearing of nerve type present since early infancy. The visual acuity was normal but there was a suspicion of some retinal degeneration seen with the ophthalmoscope. The parents were not related. The mother was normal, but the father had syndactyly of both feet. One paternal grandfather and one paternal uncle were feeble-minded and the grandfather had syndactyly of both feet.

(ix) *Scott and Johnson (1942).* Four sibs, of whom two were affected. One boy showed the complete syndrome plus deafness—apparently congenital. The other was reputed to have obesity, visual defect, mental backwardness and polydactyly, but is not recorded as deaf.

The parents are not related, but there is a history of polydactyly in the father's family.

Deafness in unaffected relatives.

This is recorded in three family groups and six individuals.

(i) *Lhermitte and Bollack (1936).* Deaf mutism in the maternal aunt of a patient showing the complete syndrome. No mention is made of consanguinity in the parents. One paternal great uncle had polydactyly.

(ii) *Novick (1939).* A family in which deafness appeared in the descendants of the affected sibship. The parents were normal and not related. There were 12 children—three normal, one with the complete syndrome, and the remainder showing one or other component in some degree, *e.g.*, obesity, mental dullness or visual defect. Of the latter, two had each a child with defective hearing, although neither of them shows the syndrome, and neither of the marriages was consanguineous. One member of the affected sibship is reported as having defective hearing, but it is not clear which.

(iii) *The present record. Family H—.*

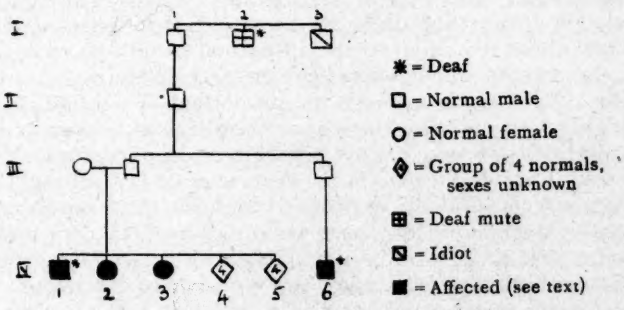

FIG. 3. The Pedigree of Herrlinger.

The Pedigree of Herrlinger (quoted by Nettleship, 1908).

This family tree extends over four generations and is of special interest as it includes cases of deafness both in the syndrome and in apparently normal antecedents.

In generation I, 2 was deaf mute and 3 an idiot. IV, 1 was an idiot, partly deaf, and had retinitis pigmentosa and polydactyly; IV, 2 was an idiot with retinitis pigmentosa; IV, 3 was also an idiot with retinitis pigmentosa and polydactyly; IV, 6, a cousin, was deaf mute and blind.

DISCUSSION

THE SYNDROME

Pathology.

The association of obesity of the pituitary type with hypogenitalism suggests an underlying pituitary or hypothalmic defect. The occurrence of other apparently related abnormalities such as diabetes insipidus and increased sugar tolerance points in the same direction. Marañon (1941) regards them all as one component—adiposo-genital dystrophy.

In reporting his finding of an excess of basophil and eosinophil cells in the anterior lobe of the pituitary, N. L. Anderson (1941) quotes two other cases with a similar post mortem finding—one of Griffith in a girl with the syndrome, and one of Stewart in a boy showing pseudo-hermaphroditism, adiposity, polyuria and hypoglycaemia. In only four cases of the syndrome has a post mortem description of the pituitary been given, and in only two is it given in detail. In both of them this finding has been made.

Genetic Data.

(*a*) *Ratio of affected to normal sibs.* Table Ia shows records of 54 complete sibships. They contain 99 affected, and 148 normal sibs. This gives a proportion of 1 : 1·49, very much higher than the theoretical 1 : 3 of a recessive defect. If the material of Cockayne and others (1935) and Sorsby and others (1939) be added, the proportion falls to 1 : 1·75. In recessive defects sibships where the children are all normal cannot be recognized, since the parents are almost always phenotypically normal heterozygotes. This tends to make the proportion of affected children too high. Various corrections have been devised to overcome this difficulty. Streiff and Zeltner (1938) have applied four of them with results varying from 30·4 per cent. affected (Weinberg) to 22·1 per cent. affected (Weinberg proband method), the mean being 26·9 per cent. Macklin (1938), using Hogben's method, corrected 28·5 per cent. The proportion is compatible with a recessive defect. It is however high, and this suggests a high rate of expression.

(*b*) *Consanguinity.* Of 57 sibships in Table I, the parents were first cousins in 11, second cousins in two, and related in other

degrees in 4. They were unrelated in 24 and not recorded as either in 16. If those not recorded are counted as unrelated, the proportion of first cousin marriages is 19·2 per cent., as compared with 0·8 per cent. in the general population (Fraser Roberts, 1940). The incidence of consanguinity of all degrees is 29·8 per cent. Cockayne (1935) found 23 per cent. in the complete sibship and 18 per cent. in all. Sorsby (1939) taking the complete sibships in which a definite statement was made, found 38·7 per cent.

(*c*) *Sex ratio.* In Table I, including the incomplete sibships, there are 102 sibs known or reputed to be affected and 148 known or reputed to be normal. Of the affected sibs, 60 were males, 35 females, and in 7 cases the sex is not recorded. Of the normal sibs, 47 were males, 42 females and in 59 cases the sex was not recorded. This excess of males agrees with the figures of Cockayne *et al.* (1935), who found 44 affected males and 28 affected females in the completed sibships, and Sorsby and others (1939) who found 33 affected males and 16 affected females. Both authors found no excess of males amongst normal sibs.

Sorsby and others (1939) tried to explain this excess of males by applying a method used by Haldane (1938) to account for the excess of males amongst albinos. Haldane held that males were more likely to come under observation than females. If this is the reason for the excess, the probands in sibships with two or more affected should be in the same sex ratio as in those with only one. On this assumption, the probands can be extracted from the former sibships and the excess of males should disappear in the secondary sibs. Sorsby and others (1939) using 80 sibships, found that it did not. In Table III, the method is applied to 175 complete fraternities—all the complete sibships of Cockayne and others (1935), Sorsby and others (1939) and all except family B— in the present review. It will be seen that although the percentage of males amongst secondary sibs is reduced, yet it is still significantly high. The excess of affected males therefore cannot be regarded as artificial.

(*d*) *Direct transmission and digital anomalies.* The only case of direct transmission of the whole syndrome is that of Laborne (1944). In this case an affected man married his second cousin, who may well have been a carrier, so that there is no evidence of simple dominance.

Single components of the syndrome however occur fairly frequently in the antecedents. Of these, the most often recorded is polydactyly (or other digital anomalies). In the literature from 1938-48, out of 57 sibships polydactyly in ascendants is mentioned in 8, obesity in 6, mental defect in 4, and visual defect of unknown cause in 2. In addition the two families of Lurie and Levy (1942)

show direct transmission of syndactyly to two and three generations respectively.

On the other hand, polydactyly is more often absent in cases of the syndrome than any other component. Of 82 cases analysed in the appendix, digital anomalies were definitely absent in 18 cases, hypogenitalism in 14, mental deficiency in 11, obesity in 6, and the retinal lesion in 3. Since the diagnosis of hypogenitalism and mental deficiency is often doubtful, as shown by the high percentage of queries in the appendix, it is probable that these figures are too high.

Polydactyly therefore would appear to be the component most frequently found in antecedents and most frequently absent in cases of the syndrome.

Polydactyly alone in the sibs of affected individuals (apart from those dying young) is only recorded in two instances, both somewhat doubtful (Laborne, 1944; D'Abreu and Ferriman, 1941).

Mode of Inheritance.

(a) *Chance association.* Warkany and Weaver (1940) hold that these cases do not constitute a true clinical entity but only a chance association of rare defects. If this were so, the condition would certainly be much rarer than it is. Radner (1940) has calculated that the chance of a single case occurring would be so slight that the syndrome could hardly have emerged at all. In fact, 102 cases have been reported in the last ten years—and many more must exist unreported.

(b) *Single gene recessive.* It has been suggested that the syndrome may be due to a single recessive autosomal mutant gene with multiple effects. This theory is strongly supported by Streiff and Zeltner (1938) and Fraser Roberts (1940).

We have seen that the proportion of affected to normal children is compatible with this idea. The high incidence of consanguinity in the parents is strongly in favour of a recessive condition. The appearance of polydactyly in the ascendants can be explained if it is assumed that the gene is incompletely recessive, and certain of its effects, notably polydactyly, appear in a proportion of heterozygotes. To explain the frequent absence of polydactyly in affected individuals, it is further necessary to assume that although expressed in a proportion of heterozygotes, it is not expressed in a number of homozygotes, whereas the other effects rarely, if ever, present in heterozygotes are expressed in a higher proportion of homozygotes. Supposing that this can be accepted, it follows that, parents of affected individuals being heterozygous, a certain proportion of them should be polydactylous. The only recorded cases are those of Lurie and Levy described above. It is clear that the single gene theory does not easily fit all the facts, although it does

account for the most important ones. It does not in itself provide any explanation of the excess of affected males.

(c) *Two gene theories*. Rieger and Trauner (1929) postulated two linked autosomal recessive genes, one responsible for the abnormalities of ectodermal origin (obesity, hypogenitalism, retinal lesion, mental defect) and the other for those of mesodermal origin (polydactyly and other skeletal abnormalities). Their view is supported by Sorsby and others (1939). Bauer (1927) regarded polydactyly as dominant and independent of the other components.

If it is assumed that one of the genes is dominant, or at any rate incompletely recessive, these theories have the advantage that the behaviour of polydactyly can be explained by dissociation of genes. They demand, however, equally with the single gene hypothesis, that a proportion of the heterozygous parents should be polydactylous. In addition, a number of the sibs of affected individuals would carry the polydactyly gene alone and in a proportion of these cases, the gene would be expressed. There are no definite records of polydactyly occuring by itself in the sibs of individuals with the whole syndrome.

Like the single gene hypothesis, these theories fit the observed facts as to the proportion of affected to normal offspring and consanguinity of parents sufficiently well. They do not in themselves provide any explanation of the excess of males any more than it does. There is little to choose then, between them; but *a priori*, a two gene hypothesis is less likely as an explanation of a rare abnormality than a single gene one.

(d) *Sex-linked theories*. Macklin (1938) has tried to explain the sex distribution by postulating a sex-linked gene. According to her theory, the syndrome is caused by one dominant autosomal mutant gene and one sex-linked recessive. It is assumed that the presence of both genes is necessary for full expression. The hypothesis faces two serious objections. In the first place, it requires five times as many families with males only affected as with females or both sexes affected. Table II shows 30 out of 57, that is approximately equality. Sorsby and others (1939) found 9 families with two and more affected males and 17 with affected children of both sexes. In the second place, the hypothesis of recessive sex-linkage in general demands that the sex incidence of the condition must be equal in sibships containing affected females. Csik and Mather (1938) applying this principle, tested the hypothesis in respect of several hereditary abnormalities. In the case of the Laurence-Moon-Biedl syndrome, they found that the excess of males could not be attributed to sex-linkage. The idea then must be rejected It may be noted that partial sex-linkage can also be rejected, as it cannot lead to a regular excess of males.

(e) *Sex limitation.* We have seen that there is a true excess of males which cannot be regarded as artificial, and that none of the genetic theories account for it. Csik and Mather (1938) have suggested a relatively low penetrance in the female. On these lines, a possible explanation might be a sex limiting autosomal modifying gene preventing expression in the female, such as Harris (1948) has suggested for multiple exostoses. Unfortunately the method he employs for testing the hypothesis cannot be readily applied to a recessive condition such as Laurence-Biedl syndrome. There is, however, an objection to this explanation. It involves a reduced penetrance and therefore the proportion of affected to normal sibs after correction should be low. It has been shown to be high. There is thus at present no satisfactory explanation for the excess of affected males.

In concluson, it may be said that the sex-linked hypothesis is untenable. The single gene recessive and two gene theories are very imperfect but the former is a priori the least objectionable.

DEAFNESS

Incidence of congenital deaf mutism in the general population.

Grant Keddie (1945) in a survey of congenital deaf mutism in Scotland from 1918-37 found an incidence of 3·88 deaf mutes per 10,000 live births. This in an incidence of 0·038 per cent. at birth. He states that this rate of incidence is certainly low since ineducable cases have been excluded.

Eichholz (1932) in a survey for England and Wales comparing the number of deaf mutes in special schools of the 15-16 age group with the general school population in the 14-15 age group gives an incidence of 1 :1,160 or 0·086 per cent.

Best (1943) gives the number congenitally deaf per 1,000,000 of the population of the United States in 1920 as 157, that is, ·0157 per cent.

As an approximation, we may take it that the incidence is in the region of 0·05 per cent.

Incidence of congenital deaf mutism in the Laurence-Biedl syndrome.

Out of a total of 178 family groups reported (including incomplete records), congenital nerve deafness has been recorded in 13, with a total of 22 individuals affected. In order to obtain a figure comparable with those given for the general population, the incidence in affected individuals or their sibs only has been taken. This excludes relatives who were only reported because they were deaf. Sibs who died in infancy so that their deafness could not

have been known, have been excluded. Where there is doubt as to the age of death, they have been included.

On this basis, out of a total of 611 members of affected sibships, 18 were deaf—an incidence of 2·94 per cent. or nearly 60 times as great as in the general population. If the cases of Boenheim, Weiss, and Lurie and Levy be excluded, as not true cases of the syndrome, and those of Attiah and El Gamal and Novick, on account of uncertainty as to the cause of deafness, 10 cases of congenital deaf mutism are left—an incidence of 1·63 per cent. or 30 times that in the general population.

THE SYNDROME WITH ITS ASSOCIATED AND ALLIED CONDITIONS

These figures suggest strongly that deaf mutism does not occur merely by chance in the Laurence-Biedl syndrome and that it is in some way related to it. It seems likely that many of the associated conditions described above are also related, and that the conditions classed as doubtful cases or allied conditions may be variants of the syndrome. Sorsby (1939) described as allied conditions a number of syndromes such as somatic and psychic infantilism with coloboma of the iris and skeletal anomalies (Biemond's syndrome); mental deficiency, hypogenitalism, Friedrich's ataxia and choroidal sclerosis; cerebellar ataxia, nystagmus, exophthalmos and brachydactyly; anomaly of stature and retinal degeneration; obesity with microphthalmos and other ocular anomalies; etc., etc. The original case reports by Laurence and Moon had no polydactyly but were dwarfed and ataxic. It is not clear what is the relation of these conditions to the syndrome and each other, but it is probably diverse. Amongst the associated conditions, for example, genu valgum and pes planus are, almost certainly secondary mechanical effects caused by excessive obesity in young persons. Nystagmus is the result of the retinal lesion. The metabolic disturbances, such as diabetes insipidus and obesity, may well be endocrine effects at second or even third hand. Other variations and complications may conceivably arise from the action of modifying genes.

In its broad outlines, the Laurence-Moon-Biedl syndrome is perfectly straightforward. It is a hereditary condition with recessive transmission. In its details it shows endless variability, seems closely related to a number of other conditions, and will not fit properly into any precise genetic scheme. The reason probably is that the underlying genetic cause is simple—a single recessive autosomal mutation—while its manifestations are rendered complex and variable by the action of secondary mechanical effects, endocrine disturbances and genetic modifying factors.

SUMMARY AND CONCLUSIONS

Two new families of the Laurence-Biedl syndrome are reported.

(1) The H— family, offspring of a first cousin marriage, consisting of two females with the complete syndrome, one female who died young, and was reputed to have had polydactyly, two male deaf mutes, two normal females and two normal males.

(2) The B— family, offspring of unrelated parents, consisting of two affected sibs only, one female showing the complete syndrome, one male lacking polydactyly.

The literature of the syndrome as a whole is reviewed over the last ten years. In addition, all case reports mentioning deafness published since 1864 are reviewed in detail.

From this survey, the following points emerge :—

(1) The incidence of congenital deaf mutism in Laurence-Moon-Biedl cases and their sibs is thirty times as high as in the general population.

(2) In the syndrome as a whole, there is an excess of affected males which cannot be explained as artificial.

(3) Polydactyly is the component most frequently present in ascendants and most frequently absent in affected individuals.

(4) What post-mortem evidence there is points to a pituitary abnormality with an excess of basophil and eosinophil cells in the anterior lobe. It is, however, very scanty.

The possible theories of inheritance are discussed. It is shown that there are serious objections to all of them and that some can be definitely rejected. The least objectionable theory is that of a single recessive autosomal mutation.

It is concluded that deaf mutism is related in some way at present unknown to the syndrome. The suggestion is made that the syndrome, with its associated conditions, and possibly allied syndromes, are due to a single recessive autosomal mutation with multiple effects, and that the complexity and variability of its manifestations are caused by secondary mechanical and endocrine factors and possibly the influence of modifying genes.

I wish to express my gratitude to Dr. Raymond Greene for his kindness in supplying the details of the B— family, and to Mr. H. E. Hobbs, F.R.C.S., for his help. I am indebted to Mr. J. E. Cole of St. Thomas's Hospital for his help in interpreting the *x*-ray films and to Dr. G. A. Lilly, Physician Superintendent of Crane Hill Hospital, Coulsdon, for allowing me to examine a member of the H— family and for supplying *x* rays.

I wish to thank Professor Sorsby for his unstinted help and encouragement and valuable suggestions.

TABLE I

(*a*) *Complete Sibships*, 1938–48

TABLE I

(*a*) *Complete Sibships*, 1938–48

Author	Total Sibs.	♂	♀	●	♂	♀	○	Consanguinity of parents	Remarks	Race or Nationality
Anderson, Graham (1948) ...	2	1	—	—	—	1	—	—	—	—
Anderson, N. L, (1941)	1	1	—	—	—	—	—	None	Two half-brothers, one half-sister reputed normal.	Greek
Attiah and El Gamal (1940) ...	3	2	—	—	—	—	—	First cousin	♂ died æt. 2. Two abortions. One affected deaf.	
D'Abreu and Ferriman (1941) ...	17	—	1	—	—	—	11	None	● four reputed blind from birth—three died young. ♀ one polydactyly, reputed normal vision, died young.	—
Demirag (1944)	5	1	—	—	4	—	—	—	—	—
Baldi (1945)	5	—	3	—	—	2	—	None	Two stillbirths.	—
Bergouignan and Viaud (1946) ...	2	1	1	—	—	—	—	None	—	—
Bernard and Chassagne (1938) ..	2	1	—	—	—	—	—	—	♀ twin died æt. 3, reputed normal.	—
Beato Forn (1940)...	10	—	1	—	—	—	9	Yes	Mother is the daughter of her husband's first cousin.	—
Borsotti (1939)	6	2	—	—	—	—	2	First cousin	● died young. Reputed to have polydactyly. ○ died young. Reputed normal.	—
Bregeat (1947)	1	1	—	—	—	—	—	—	—	—
Cavallaci (1939)	3	1	—	—	—	2	—	None	One of the normal sisters is dead but reputed normal.	—
Corcelle and Berthon (1939) ...	2	—	1	—	1	—	—	—	—	—
Delmas-Marsalet et al (1938) ...	1	1	—	—	—	—	—	Yes	Mother married her half-sister's son.	—
Ellis and Law (1941)	4	—	1	—	—	2	—	None	One ♂ died at birth—reputed normal. One of the reputed normal sisters was known to have tuberculosis and to be M.D.	—
Grant and Smith (1942)	5	—	1	—	—	—	4	—	Two of the normal sibs. were fat.	—
Garcin et al (1945)	2	1	—	—	—	1	—	First cousin	—	—
Kielholz (1946)	2	—	1	—	—	1	—	None	—	—
Kloess (1941–2)	4	1	—	—	—	3	—	None	—	—
Krarup (1939)	2	1	1	—	—	—	—	None	The affected brother is only recorded as having polydactyly and cryptorchidism.	
Kutumbiah and Abbu (1942) ...	5	1	—	—	1	2	—	First cousin	♂ died æt. 1, reputed normal.	Indian
Laborne (1944) (i)	5	1	—	—	2	—	—	None	Two ♂ died young reputed normal.	—
,, ,, (ii)	3	1	1	—	1	—	—	Second cousin	Children of affected male in (i), by his second cousin. The affected boy had polydactyly only.	—
Likins et al. (1947)	8	1	1	—	—	—	5	——	● died young—reputed to have had polydactyly.	—
Lurie and Levy (1942) (i) ...	6	1	—	—	2	3	—	None	Affected male deaf.	

TABLE I—(*continued*)

Author	Total Sibs.	♂	♀	●	♂	♀	○	Consanguinity of parents	Remarks	Race or Nationality
Lyle (1946) (i)	3	—	1	—	1	1	—	—	—	—
,, ,, (ii)	2	—	1	—	—	—	1	—	—	—
Marmor and Lambert (1938) (i)...	1	1	—	—	—	—	—	None	—	—
,, ,, ,, ,, (ii)...	2	1	—	—	1	—	—	First cousin	Unaffected brother was dull.	—
Marques (1941)	10	1	—	—	—	—	9	None	Seven of the sibs. reputed normal had died of unknown causes.	—
McCullagh and Ryan (1941) ...	5	4	—	—	1	—	—	First cousin	—	—
Montanaro and Turro (1942) ...	3	—	2	—	—	—	—	Yes	Maternal great grandmother and paternal grandmother were sisters. ♂ dead—reputed to have polydactyly.	—
Morgensen (1941)	4	1	—	—	2	1	—	First cousin	The unaffected sister has hydrocephalus.	—
Muthayya and Iyer (1939) (i) ... (Quoted by Kutumbiah and Abbu, 1942)	6	2	—	—	2	1	—	—	One ♂ had polydactyly (?) died young. One of the unaffected boys was dull.	Indian
Novick (1939)	12	—	1	—	5	6	—	None	Of the unaffected sibs. four were normal, four were dull and/or had visual defect, three were obese. One was deaf and two had deaf children.	—
Parella (1938)	6	2	—	—	1	—	—	None	One ♀ one ♂ died young, reputed affected.	—
Radner (1940)	6	—	2	—	2	—	—	None	One ♂ died young, reputed to have had polydactyly. One ♀ died young, reputed to have had polydactyly and atresia ani.	—
Rathmell and Burns (1938) ...	11	1	1	—	2	3	—	First cousin	One ♂ (?) affected, not seen. One ♂ died young (?) affected. One ♂ died young (three weeks). One ○ died young (first year).	Russian Jews
Rojas Loa (1939)	2	1	—	—	—	1	—	—	—	—
Roth (1947)	6	4	—	—	1	1	—	None	The unaffected sister was obese.	Americans of Czecho-slovak origin
Ruggeri (1938)	5	2	1	—	—	—	—	Second cousin	Two ♂ died young, reputed to have had polydactyly. One abortion.	—
Schwartz and Boudreau (1940) ...	9	1	—	—	2	1	—	—	Four ○ died young, cause unknown. ○ died æt. 2, scarlet fever. One still-birth.	—
Scott and Johnson (1942) ...	4	1	—	—	—	—	2	None	One affected brother was not seen but was reputed to have obesity, visual defect, mental defect, and polydactyly. ♂	Negro one affected deaf.

TABLE I—(*continued*)

TABLE I—(*continued*)

Author	Total Sibs.	♂	♀	●	♂	♀	○	Consanguinity of parents	Remarks	Race or Nationality
Snell (1942)	8	—	2	—	1	4	—	None	♀ died æt. 8, reputed to have had obesity and polydactyly.	Negro
Taylor, (1947)	1	1	—	—	—	—	—	None	One sister still-born, reputed to have had polydactyly and part of head missing.	—
Urechia et al (1939)	8	1	—	—	—	—	—	None	Six ○ died in infancy. ● died in infancy, reputed to have had polydactyly.	—
Vraa-Jensen (1945)	2	2	—	—	—	—	—	First cousin	—	—
Wang (1945)	3	—	1	—	2	—	—	—	—	—
Warkany and Weaver (1940) ...	1	1	—	—	—	—	—	—	—	—
Wendt (1941)	4	1	—	—	—	—	3	None	—	—
Wolff (1938) (i)	2	1	—	—	1	—	—	First cousin	—	—
,, ,, (ii)	4	1	—	—	1	—	—	—	Two ♀ died young.	—
Present record. H-family ...	9	—	2	—	4	2	—	First cousin	♀ died young, reputed to have had polydactyly. Two unaffected deaf.	English
,, ,, B-family ...	2	1	1	—	—	—	—	None	—	—
	247	51	28	—	41	38	46			
			79			125				
Died young, probably affected ...		7	4	6	—	—	—			
Not seen, ,, ,, ...		2	—	1	—	—	—			
Died young, ,, normal ...		—	—	—	6	4	13			
		60	32	7	47	42	59			
	247		99			148				

(*b*) *Incomplete Sibships*

Author	♂	♀	Consanguinity of parents	Remarks	Nationality
Lurie and Levy (1942) (ii)	—	1	None	Nerve deafness.	—
Lyle (1946) (iii)	—	1	—	—	—
Muthayya and Iyer (1939) (ii) ... ... (Quoted by Kutumbiah and Abbu, 1942)	—	1	Yes	Mother married maternal uncle.	Indian
Total	—	3	—	—	—

♂♀—affected; ♂♀—normal; ●○—sex not stated.

TABLE II.—*Nerve Deafness in relation to the Laurence-Biedl Syndrome*

1. Deafness in cases of the syndrome.

Author	Partial Syndrome	Complete Syndrome	Total
Boenheim, 1929	2	—	2
Weiss, 1932	2	—	2
Steinberg, 1937 (1)	3	—	3
,, ,, (2)	1	—	1
Becker, 1937...	1	—	1
Attiah and El Gamal, 1940 ...	—	1	1
Lurie and Levy, 1942 (1)	1	—	1
,, ,, ,, ,, (2)	1	—	1
Scott and Johnson, 1942	—	1	1
Herrlinger (Nettleship, 1908) ...	—	2	2
Total	11	4	15
Total number of Laurence-Moon-Biedl cases reported 1864-1948, including cases probably affected			275

2. Deafness in unaffected relatives.

Author	Number
Lhermitte and Bollack. 1936	1
Novick, 1939	3
Herrlinger (Nettleship, 1908)	1
Present record	2
Total	7

TABLE III.—*Complete Sibships for correction of Sex Ratio.*

Number with Laurence-Moon-Biedl Syndrome		
	1	1 male: 73. 1 female: 37.
	2	2 males: 16. 1 male + 1 female: 19. 2 females: 6.
	3	3 males: 3. 2 males + 1 female: 7. 1 male + 2 females: 4. 3 females: 2.
	4	4 males: 2. 3 males + 1 female: 2. 2 males + 2 females: 4. 1 male + 3 females: 0. 4 females: 0.

	Male	Female	Percentage Males	Secondary Males	Secondary Females	Percentage Males in second sibs.
1	73	37	66·3	—	—	—
2	51	31	62·1	23·9	17·1	58·2
3	27	21	56·2	16·4	15·6	51·2
4	22	10	68·7	16·7	7·3	69·5
Total	173	99	63·6	57·0	40·0	58·7

Including all the complete sibships reviewed by Sorsby, Avery, and Cockayne (1939), Cockayne, Krestin, and Sorsby (1935) and the present review (excluding family B—).

APPENDIX A

Incidence of Individual Components (cases reported 1938–48)

Author	Digital Anomalies	Retinal Lesion	Obesity	Hypo-genitalism	Mental Defect	Remarks
D'Abreu and Ferriman (1941)	—	+	?	+	—	
Anderson, Graham (1948) ...	+	+	+	—	—	
Anderson, N. L. (1941) ...	+	?	+	+	+	Lens opacities
Attiah and El Gamal (1940) (i)	+	+	+	+	+	
,, ,, ,, ,, ,, (ii)	+	+	+	+	?	
Baldi (1945) (i)	+	+	+	—	+	
,, ,, (ii)	—	+	?	—	+	
,, ,, (iii)	+	+	+	?	?	
Beato Forn (1940)	+	?	+	?	+	
Bergouignan and Viaud (1946) (i)	+	+	+	?	—	
,, ,, ,, ,, (ii)	—	+	+	+	?	
Bernard and Chassagne (1938)	+	—	+	+	—	
Borsotti (1939) (i)	+	+	—	—	—	Macular defect
,, ,, (ii)	—	+	—	—	—	,, ,,
Bregeat (1947)	+	+	+	+	+	
Cavallaci (1939)	+	+	+	+	?	
Corcelle and Berthon (1939) ...	?	+	+	?	+	Polydactyly not mentioned
Delmas-Marsalet et al (1938) ...	+	+	+	+	+	
Demirag (1944)	+	+	+	+	—	
Ellis and Law (1941)	—	+	+	+	—	
Garcin, Mann, and Piguet (1945)	+	+	+	+	+	
Grant and Smith (1942) ...	+	+	+	?	+	
Kielholz (1946)	+	+	+	+	+	
Kloess (1941)	—	+	+	+	+	
Krarup (1939)	+	+	+	+	+	
Kutumbiah and Abbu (1942) ...	+	+	+	+	+	
Laborne (1944) (i)	—	+	+	?	—	
,, ,, (ii)	+	—	—	—	?	Children of (i) by his second cousin
,, ,, (iii)	+	+	+	?	?	
Likins, Scott, and Handelman (1947) (i)	+	+	+	?	+	
Likins, Scott, and Handelman (1947) (ii)	+	+	+	?	+	
Lurie and Levy (1942) (i) ...	+	—	+	?	+	Deaf. Not related to (ii)
,, ,, ,, ,, (ii) ...	+	?	+	+	+	Deaf. Not related to (i)
Lyle (1946) (i)	+	+	+	—	—	
,, ,, (ii)	+	+	+	?	+	
,, ,, (iii)	+	+	+	+	+	
Marmor and Lambert (1938) (i)	+	+	+	+	+	
,, ,, ,, ,, (ii)	+	+	+	+	+	
Marques (1941)	+	+	+	+	+	
McCullagh and Ryan (1941) (i)	—	+	+	?	+	
,, ,, ,, ,, (ii)	—	+	+	?	+	
,, ,, ,, ,, (iii)	—	?	+	?	?	
,, ,, ,, ,, (iv)	—	+	+	—	+	
Montanaro et al (1942) (i) ...	+	+	+	?	+	
,, ,, ,, (ii) ...	+	+	+	?	+	
Morgensen (1941)	+	+	+	?	+	
Novick (1939)	+	?	+	+	+	Deaf descendants. Unilateral optic atrophy
Parrella (1938) (i)	+	+	+	+	+	
,, ,, (ii)	+	+	+	+	+	
Radner (1940) (i)	+	+	+	+	+	
,, ,, (ii)	+	+	+	+	+	
Rathmell and Burns (1938) (i)	+	+	+	+	+	
,, ,, ,, ,, (ii)	+	+	+	+	+	

APPENDIX A—(*continued*)

Author	Digital Anomalies	Retinal Lesion	Obesity	Hypo-genitalism	Mental Defect	Remarks
Rojas Loa (1939)	+	+	+	+	+	
Roth (1947) (i)	—	+	—	+	+	
„ „ (ii)	—	+	—	+	?	
„ „ (iii)	—	+	+	+	?	
„ „ (iv)	—	+	+	+	—	
„ „ (v)	+	+	?	—	+	
Ruggeri (1938) (i)	+	+	+	+	+	
„ „ (ii)	+	+	+	+	+	
„ „ (iii)	+	+	+	?	?	
Schwartz and Boudreau (1940)	+	+	+	+	+	
Scott and Johnson (1942) (i)	+	+	+	+	+	Deaf.
„ „ „ „ (ii)	+	+	+	?	+	Reputed—not examined
Snell (1942) (i)	+	+	+	—	+	
„ „ (ii)	+	+	—	—	—	
Taylor (1947)	+	+	+	+	+	
Urechia et al (1939)	+	+	+	+	+	
Vraa-Jensen (1945) (i) ...	+	+	+	—	+	
„ „ (ii) ...	+	+	+	—	+	
Wang (1945)	+	+	+	+	+	
Wendt (1941)	—	+	+	+	?	
Warkany and Weaver (1940)	—	?	+	+	+	Microph-thalmos
Wolff (1938) (i)	+	+	?	+	?	
„ „ (ii)	+	+	+	+	+	
Present record. H—Family (i)	+	+	+	—	+	Two brothers deaf mute
„ „ „ (ii)	+	+	+	—	+	Two brothers deaf mute
„ „ B—Family (iii)	+	+	+	+	+	
„ „ „ (iv)	—	+	+	+	+	
Muthayya (Quoted by Kutumbiah and Abbu, 1942) (i) ...	+	+	+	+	+	
Muthayya (Quoted by Kutumbiah and Abbu, 1942) (ii) ...	+	+	+	+	?	
Total —	18	3	6	14	11	
„ ?	1	6	4	20	13	
„ + ...	63	73	72	48	58	
	82	82	82	82	82	

Cases in which the record leaves any doubt as to the presence or absence of a component have been marked ?

Members of the same sibship are bracketed

APPENDIX B

Cases in which Basal Metabolic Rate is recorded

Author	Percentage	
Likins et al (1947)	—6	
Lyle (1946)	—8	—28
Attiah and El Gamal (1940)	—20	—22
D'Abreu and Ferriman (1940)	+14	
Kielholz (1946)	—21·2	
Montanaro et al (1942)	—16	—18
Wendt (1941)	—4	
Ruggeri (1938)	—2	
Wolff (1938)	—21	+1·6

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VISUAL ACUITY WITH BRIEF STIMULI*

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INTRODUCTION

ALTHOUGH the visual acuity of the eye has been often investigated, it has not yet been examined very fully in conditions of limited exposure time. The only known previous investigations in this field are those of Graham and Cook (1937), and Nivén and Brown (1944), apart from a similar investigation on the somewhat analogous problem of intensity discrimination at short exposure times by Graham and Kemp (1935). The experiments here described aimed at increasing the intensity range beyond those of previous observations. They are all concerned with exposures of less than one second. The work can still only be regarded as incomplete; many more sets of observations with many more observers would be necessary before any accurate picture could be drawn of the variation of visual acuity under the various limiting factors which can be imposed, and over the whole possible range of exposure times. Meanwhile it is hoped that these results will facilitate the arrangement of further work. The experiments fall into two parts; in which differing test objects were used:

(*a*) A double-star type of test object, with dark adaptation.
(*b*) A grating type of test object with low light-adaptation.

In both cases the object is bright on a dark-field, the contrast being effectively " minus one ".

THE DOUBLE-STAR OBJECT

A consideration will be given later of the relative merits and drawbacks of this type of test object. It consists of a pair of circular holes each 0·59 mm. in diameter drilled in a thin opaque screen, with a third hole of 0·83 mm. diameter mid-between the other two. This third hole could be exposed when the other two were obscured, and *vice versa*, by means of a movable shutter in front of the plate. This was to provide an " alternative presentation " to the double-star presented by the other two holes, namely a single " star " of area equal to the sum of the areas of the other two (in order to avoid the photometric factor in the interpretation of any observation). The double-star distances (centre to centre)

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were made to subtend angles at the observing eye ranging from 3 mins. of arc down to 1 min. of arc. The latter separation of the holes was always horizontal. The exposure of the light behind it was made by a calibrated Compur shutter, having speeds ranging from 1/2 to 1/300th sec. The light source was a filament lamp, maintained at constant amperage, giving the test object, regarded as a source, a maximum effective brightness (*i.e.*, allowing for filters, etc.) of 58·15 candles/sq. ft. of test object, or $6{\cdot}2 \times 10^{-2}$ stilb. Intensity control below this maximum brightness was by means of a calibrated pair of Nicol prisms.

The observer's position was 20 feet from the test object, except for the observations for test objects subtending below 2 mins. of arc, for which the distance was increased; this was admittedly a possible source of criticism in that an unnecessary variable was thus introduced into the otherwise constant conditions of the experiment. The time available to the observer (K) did not, however, permit of the construction of the various additional test objects which would have been desirable. The observations were made with the right eye, using an artificial pupil of 2·5 mm. diameter and his required spectacle lens correction (−0·5D). The left eye was blacked out by means of an eyeshield. The observer's head was kept steady by means of a dental clamp. The spectral composition of the light source was limited by means of a yellow-green filter. To facilitate fixation of the eye upon the desired spot a dimly illuminated ring, the diameter of which subtended about 2° in the visual field, was exhibited, the eye being fixated on the centre of this. The image of the ring was projected into the plane of the test object by an unsilvered mirror, a gap in which allowed the unhindered observation of the object. An exacting effort at fixation was required; moreover it appeared that the observer's ability to fixate varied from day to day; so much so that on certain days, despite apparent good health and willingness on his part, he was unable to control his fixation adequately. Work was discontinued if marked fatigue set in during a run of observations.

Observations were made in groups of ten flashes, each consisting of six double-star flashes and four single-star flashes given in a random order by the operator at the test-object end of the apparatus. The observer was allowed to give a " not seen " signal and have the flash repeated if he desired. He thus gives ten actual answers of " double " or " single ".

For a given speed of flash and test object, sets of ten such flashes were made at various brightness levels, and a graphical interpolation was made to find the brightness level for which the probable " number right out of ten " would be six; this was regarded

as the brightness of the test object for the threshold of resolution, at that particular speed.

The results thus obtained may best be given in graphical form, by plotting log α t, that is the log of " visual angle *times* time of flash ", against *log* brightness. These are given in Fig. 1. A number of observations were also made up to 6° away from the fovea; the results, though rather few in number, were similar to

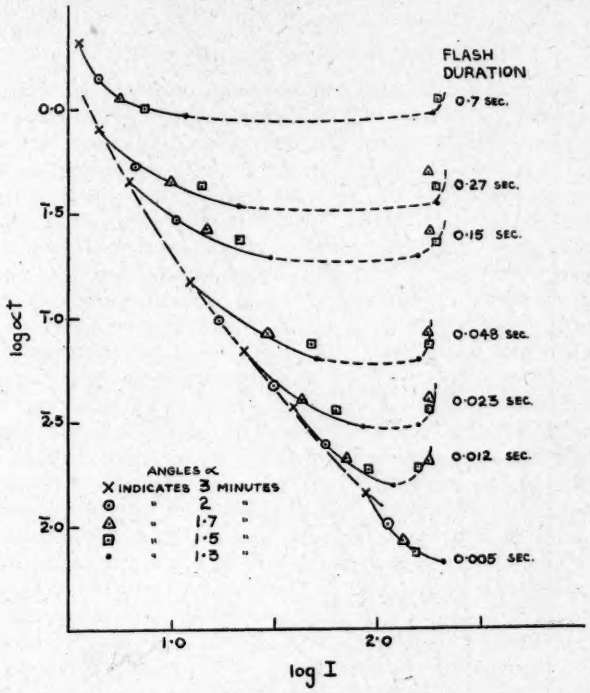

FIG. 1.

those of Fig. 1. They indicated a gradual decrease in visual acuity at angles up to 1° off-fovea, after which the decrease becomes much more rapid. Fixation is clearly the chief uncertainty. Thus, other factors remaining constant, it appears that the variation of flash visual acuity with distance from the fovea over this range is likely to be similar to that of normal long-term visual acuity; more observations would be necessary before any precise conclusions are possible.

Referring to Fig. 1 it will be noticed that the limiting visual

angle falls a little below 1·3 minutes; it was never found, however, to fall as low as 1·1 minutes for any level of the brightness. Resolution is poorer at high brightness levels presumably owing to an " over exposure " or glare effect, as will be discussed below,

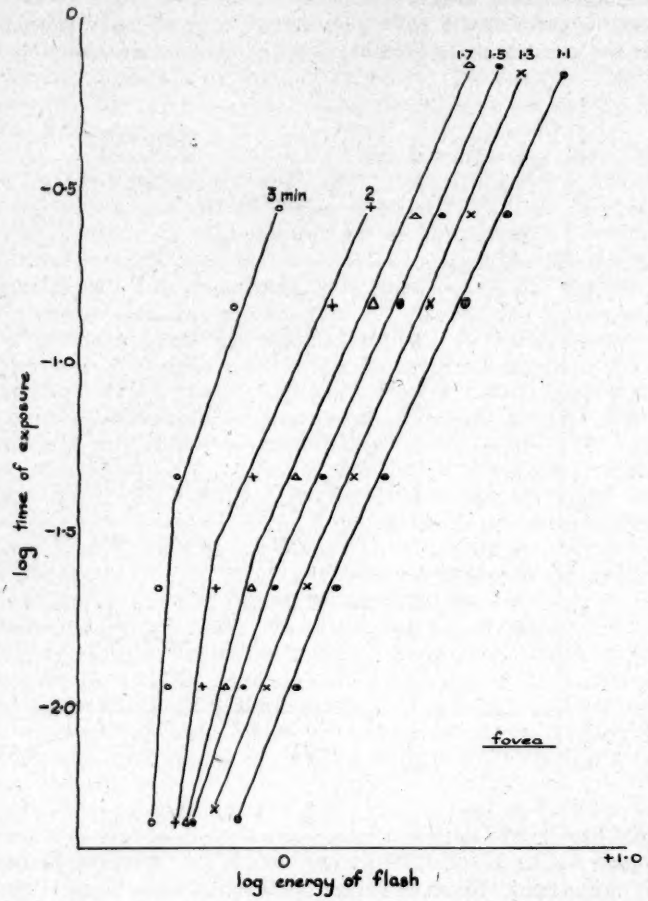

FIG. 2.

but in the intermediate levels the limit is presumably set by the imperfections of the optical image or by the retinal grain.

If the above results are used to plot curves (Fig. 2) of log (brightness *times* time) *i.e.*, *log* " energy of flash " against *log*

"time" for given visual angles, it appears that there is an approach to reciprocity between brightness and time for the 2 min. and 3 min. objects for stimulus durations up to about 0·04 seconds, but this is not the case for the smaller angles. These results do not include those of the glare region.

The optimum acuity seemed unexpectedly good for a flash exposure, and suggests that movements of the retinal image in ordinary acuity observations do not play a major part in determining the limit.

THE GRATING OBJECT

The main intention of this set of observations was not only to repeat some of the observations (using, however, a different object) but at the same time to extend the range of brightness of test object as far as possible. The first results above (Fig. 1) extended up to a high-brightness value where visual acuity appeared to be decreasing due to the "glare" effect of the bright test object against the dark background. When attempts were first made with the higher brightnesses, the star type of test object being still used, it was found that the observer could (after a little experience) learn to judge whether the flash showed a double or single star by the apparent outline of the glare patch; the patch due to a single star had more pronounced "spikes" than that due to a double star, the latter being particularly lacking in these glare "spikes" at the sides of the patch. Even without considering the precise mechanism by which such a difference in appearance could occur, it seemed manifest that it represented an additional complication in the test which is not only undesirable, but also liable to give very misleading results, since for one thing it involves a judgment of the overall width of the glare patch, which is greater than the angular subtense of the double stars themselves.

Consideration was therefore given to the possible alternatives to the double-star test object, a decision being made in favour of the Foucault grating. This could be made continuously variable in angular subtense by rotating it about an axis parallel to the bars, and, moreover, this variation itself could be used to provide an alternative presentation (which should not be resolvable) merely by rotating the grating to an angular subtense below that which can be resolved by the eye. The grating is, of course, viewed through an aperture of constant angular width*. It was expected (and found true) that the "shape of glare patch"

*It was considered desirable to avoid the type of test object whose orientation has to be judged (such as that used by Niven and Brown, 1944) because of the possibility that the astigmatism of the eye (which it is very difficult to correct completely) might require a much greater number of observations to obtain a satisfactory statistical analysis.

criterion would not be applicable here. The well-known possible drawback of the grating (*i.e.*, the possibility of reappearance of an image on the retina with reversed (but very feeble) contrast after an initial disappearance with increasing rotation) need hardly be feared in these experiments, unless the imperfections of the eye play the major part in limiting acuity, and the elementary image has certain special characteristics. Other apparent advantages and disadvantages over the double-star test object arose because the grating has a considerably larger area than the double-star. Advantages may be noted as follows:

(1) Any small unevenness in manufacture or in cleanliness of the test object itself, or in the eye (such as "*muscae volitantes*" or blood cells on the retina) would probably have less effect on the result as a whole.

(2) It was found easier to tell whether fixation was adequate with a grating flash. This point will be discussed in more detail in a subsequent section.

There are, however, certain drawbacks and difficulties:

(1) As will be explained, it was decided to introduce a dimly illuminated background. The area of the test object itself forms an appreciable and important part of this background which it is difficult to illuminate. This difficulty was overcome for practical purposes by making the bars of the grating white and illuminating them to such a brightness that this region appears (during adaptation) to be of the same even brightness as the rest of the background.

(2) At high brightness the after-images were more troublesome; but it was found that the observer could, by careful training, learn to decide whether he had resolved the actual flash or merely the after-image. There is, however, some degree of uncertainty in this connection. A longer time had to be allowed between flashes at these high brightnesses.

(3) Since a larger area of the shutter is used, its efficiency becomes important, as, especially at shorter exposures, a shutter of the type used tends to give a longer exposure at the centre relative to the periphery. This was found in fact to cause the threshold brightness to vary slightly over the area of the test object, so for example at the low-brightness threshold the observer was resolving only the central part of the grating, and *vice versa* at high brightness.

(4) In order to keep the intensity of the flash constant irrespective of the angular subtense, the area of the flash is kept constant and hence the number of lines varies. There is experimental evidence that with a small number of lines in a grating the visual acuity varies slightly with this number of

lines; hence on this score it would be desirable not to allow the effective number of lines to go much below a minimum of say six.

(5) A large area of the fovea is involved. A compromise has to be made in this respect, especially if it is the aim to investigate the variation of flash acuity over the retina. The angular subtenses of the fields are given below.

Other significant changes in the apparatus as compared with the star experiments were as follows:

(1) The maximum effective brightness of the test object was much increased by using a " Point-o-lite " lamp, neutral density filters in place of the Nicol prisms, and a lens to concentrate the light so that the observer had the condition of " Maxwellian views ". The maximum possible background brightness for the dark lines of the grating was 4,240 candles/sq. ft., *i.e.*, 4·56 stilb.

(2) The observer's position was kept at the distance of 20 feet from the test object throughout the observations.

(3) A wide adapting field of brightness 0·0051 equivalent foot-candles, *i.e.*, $1{\cdot}5 \times 10^{-6}$ stilb. was employed.

PRELIMINARY INVESTIGATION

In these experiments it was usual to fix two of the variables, *viz.*, time of exposure (t) and brightness of the test object, and find the angle through which the grating needed to be turned from the full-on position in order to obtain a 50 per cent. chance of resolution of the grating. Two gratings were required to cover the full range. The fixed area of the test object subtended about 11 minutes in the field of view.

It was found possible for the operator to obtain the required setting of the grating by " bracketing " above and below the desired position in steadily decreasing steps, until after sufficient flashes (about 40 on average) the position had been obtained, generally to a repeatable accuracy of about 1°.

The steps were not always made alternately above and below the desired position, but were occasionally mixed, to ensure that the observer was not tending automatically to give responses of " resolved " and " not resolved " alternately.

The results obtained in this set of observations were intended to be exploratory. They are given in graphical form in Fig. 3. Each curve relates to the stated time of exposure; some of the limiting angles are entered on the diagram.

The abscissae are the *logs* of the field brightness in candles/sq. ft. The observer (G.H.) required a -1D correcting lens, agreeing with his normal spectacle prescription. He reports resolution at very small limiting angles, sometimes even lower than 0·75 min., and this general level of resolution (<1 min.) persists over a range

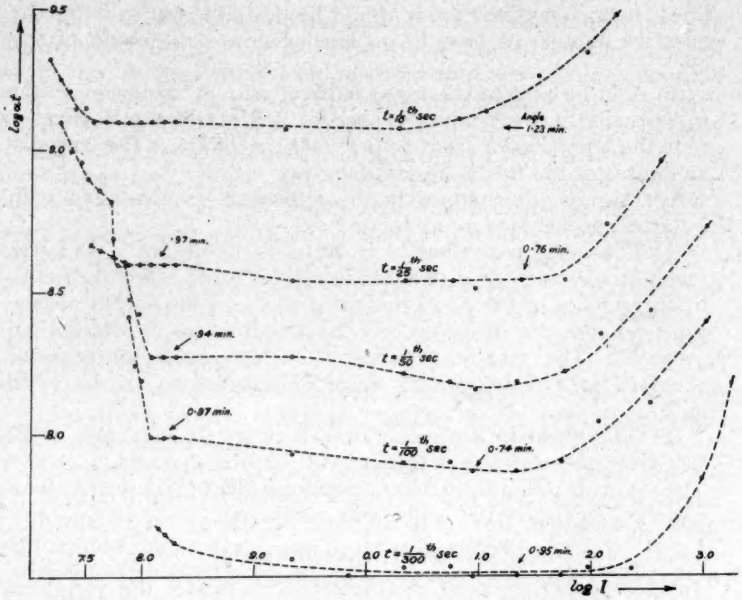

FIG. 3.

of brightnesses having a ratio of 10,000 to 1. The limiting angle formed with a grating might be expected to be smaller, on statistical grounds, than that found with a double-star. The kinks in the left-hand branches of his curves are noteworthy, but it would be difficult to say whether optical aberration or retinal grain is the limiting factor in the flat parts of the curves.

FULLER INVESTIGATION

The consistency of the exploratory observations made, indicated the possibility of allowing the observer himself to set the grating by suitably arranged remote control, and so arrive at the desired position much in the same way as setting a pointer on a scale. This scheme was adopted for further work, the " observer " being able to increase or decrease the angle of the grating by means of an electric motor. He was not able, of course, to read the actual value of the grating angle during such an observation, although he could judge by the sound of the motor itself roughly by how much he was increasing or decreasing this angle.

A means was also provided for the observer to set and to release the shutter. The latter step was considered a desirable improvement in any case, since the observer, able to release the shutter in his own time, would be likely to be in a more consistent state

of readiness. With the old method, despite the preparatory word " ready " from the operator, there was still a possibility that there was more or less " tenseness " during the short period of expectation.

The shutter was released by means of a solenoid actuated by a press button on the observer's table.

The results obtained in this set of observations by D.D. are in graphical form in Fig. 4. He had some trouble to determine

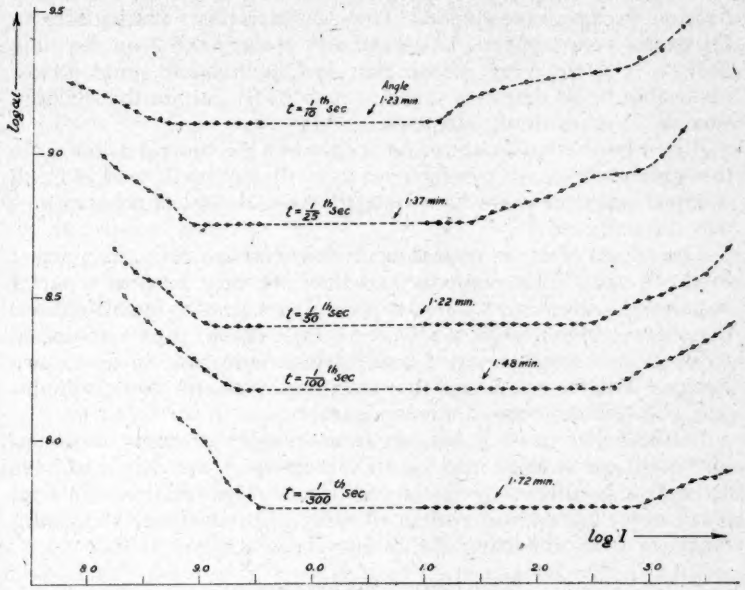

FIG. 4.

his best correcting lens for the size of artificial pupil, which was −3·5 D.Sph. His normal correction was −3·25 D/+1D Cyl. Ax 90°, and a certain small amount of irregular astigmatism seems to be indicated.

The fixed area of the test object seen by the observer subtended about 7·5 minutes. It was reduced from the previous observations in the hope of obtaining greater accuracy by reducing the area of the fovea used, even though the number of lines fell to a value of 3 when the grating was most nearly full on, *i.e.*, considerably below the desirable minimum in these extreme cases. It will be noticed at once that D.D. finds limits for the smallest angle of resolution, about double those found by G.H. It is thus possible

that the residual aberrations of D.D.'s eye are controlling the limit. Although the observer did not persist in observations when feeling perceptibly tired or unwell, he found that there was quite a high proportion of observing days when his performance was less than the optimum. There was sometimes a barely perceptible deterioration, but there were occasions when the observer had difficulty even in resolving a 3 min. subtense test object flashed for 1/10th sec. at optimum brightness. It appeared that the mechanism by which the performance was lowered was that fixation became inadequate. This was manifest, particularly in the grating experiments, as a kind of " comet's tail " on the main flash. For the very reason that lack of fixation could almost invariably be so detected, it is felt reasonably certain that fixation was at all other times adequate.

Any observations exhibiting a perceptible deterioration from the normal level of consistency were disregarded, and if such observations were more than isolated cases, the set of observations was discontinued.

The effects of improvement with practice were certainly present in the " star " observations, and they are very hard to separate in assessing the results. In the preliminary grating investigation, the observer took about a month to settle down, then a comparatively rapid complete set of observations was made in about two weeks. Thus it was hoped that such improvement, though doubtless still present, was not very marked.

In the fuller grating investigation, repeats of many observations were continually made until the observer was found to have arrived at a sufficiently static condition. The order of the final set of observations was varied, in order to prevent any remaining tendency from distorting the curves as a whole.

THEORETICAL DISCUSSION

It is well understood that visual resolution (acuity) is intimately related to intensity discrimination, since the aberrations of the optical system of the eye, diffraction, irradiation and other causes produce a degradation of the contrast of the retinal image which is more severe, the smaller the detail (Selwyn and Tearle, 1946). The finite size of the elements of the retinal mosaic is another factor capable of limiting acuity under certain conditions. In this connection it was thought that the slight involuntary movements of the eye recently confirmed by Lord and Wright (1949) might play a profound part in sustained vision. Flash stimuli should simplify the conditions here. (As mentioned above the experiments suggest that such movements are *not* of much importance.) There are some circumstances, certainly in regard to scotopic

thresholds, where the quantum characteristics of weak stimuli have to be taken into account, but no theory can progress far without a discussion of the effects in the eye and associated neural structures since, for example, visual acuity has an obvious significance in flash conditions, and even in after-images, when the perception of resolution may occur when the stimulus has ceased. The theoretical considerations given below are largely confined to photo-chemical considerations; in view of the known complexity of the visual process and the electrical phenomena of the discharges in the optic nerve fibres, some apology seems to be necessary for such a restriction, and for the very speculative application of the theory to deal with the phenomena of brief flashes.

There is weighty evidence to show that the first reaction in the process of scotopic vision is the absorption of light by the chromophore groups of the rhodopsin or similar molecules which are supposed to be associated with protein layers in the outer segments of the retinal rods.

The main evidence for this conclusion is the close correspondence between the absorption co-efficient for visual purple in solution and the spectral sensitivity of the dark-adapted parafoveal retina. No generally acceptable theory of the manner in which the initial photo-chemical change is transformed into the rhythmic nerve-pulses has yet, so far as we know, been proposed. In his well-known experiments with *Limulus*, Hartline (1935) has shown that though an interval of the order of 0·1 seconds may elapse between a flash stimulus and the onset of the nerve discharges (and this interval will be greater with diminishing stimuli) there is a good reciprocity between the duration and intensity of short stimuli, so that the number and frequency of the pulses are a function of the energy in the flash. This is an additional and important indication of the initial photo-chemical storage, and probably of fairly close conservation of the energy in passing through its different stages; if " leakage " occurs it must be of a very regular character. There is evidence to show that the absorption of as few as five quanta can give rise to a perception of light in the dark-adapted human retina and this again suggests a high degree of conservation of the photo-chemical energy.

Possibly, even the absorption of a single quantum by a rod receptor with the decomposition of a single molecule of the visual purple may give rise to a definite energy pulse in the associated neuron. The reason for the time delay, a long one when one considers the usual time scales of molecular reactions, is an interesting puzzle; it might indicate some diffusion or electro-phoresis of the excited molecules or ionic products of decomposition; it has also been suggested that an excited chromophore group may give

rise to a chain of secondary reactions leading to the excitation or decomposition of further molecules. Though our present suggestion is little more than speculation it seems possible that a rod with its presumably regular structure of protein and carotenoid molecules might act as a unit in which energy exchanges or ionic transfer can take place. The action of light would ionize some molecules and excite electrons to higher energy levels in others. Energy might then be stored in local electrostatic fields and mechanical strains; spontaneous energy exchanges between excited molecules may lead to further ionization and consequent polarization; a certain proportion of excited molecules will thus continually return to ground levels. Some of the properties of such a system, reciprocity for medium stimuli for example, would resemble those of a silver halide grain in a photographic plate. We return to this point below. The immediate point of importance is the probable conservative connection between the energy in the flash and the magnitude of the response in the nerve, in spite of the time delay. The above considerations are mainly related to rod vision, but there are many considerations, well-known and otherwise (Dartnall, 1948), which suggest that the initial phase in photopic vision is also photo-chemical, the sensitive substance still being rhodopsin; the relative spectral response being modified by the accumulation of decomposition products. This again is consistent with the Talbot-Plateau law and other phenomena of photopic vision. We therefore have some ground for discussing the photo-chemical actions in the present connection. Hecht (1935) and his collaborators have given much attention to the consequences of a theory of a simple photo-chemical system in which the decomposition products A, B, C, etc., of some initial substance S eventually re-combine to form S once again. This may be useful, insofar as it may serve to examine certain overriding effects and limits.

Let us assume that there is a rough proportionality between the limiting angle of resolution and the limiting fraction of discrimination dI/I. We may then discuss the probable limits of dI/I under flash conditions. Following Hecht (1935) let the original concentration of S be a and the general concentration of the photo-products A, B, C, at any time t be x. Then the magnitude of the visual effect is usually associated with x. However, reconstitution of S is supposed to be a function of x. The equation is:—

$$\frac{dx}{dt} = k_1 I (a - x)^m - k_2 x^n$$

where k_1 and k_2 are constants, and m and n represent the chemical order of the reaction, *e.g.*, mono-molecular, bi-molecular, etc.,

Hecht (1935) applied this equation to deal with the steady states of full adaptation. Graham and Kemp (1935), in a modification of the theory, supposed that in a given critical time $\triangle t$, during which storage might take place, the building up of a critical concentration difference δx is the criterion for the perception of a flash in which the stimulus is momentarily increased above the existing adaptation level. It is supposed that $\triangle t$ is very short in comparison with the effective adaptation time. They thus obtain a further equation which is in agreement with the general features of their experimental results. Niven and Brown (1944), assuming that visual resolution is proportional to intensity discrimination, find their results on acuity can be represented in a similar way. In our work the adapting field has a small or negligible intensity, and the conditions of flash illumination require the formal integration of some equation such as that above. In order to study some general implications we may assume very simple numerical constants. Suppose $k_1=k_2=m=n=a=1$.

Then

$$x=I\,[1-\text{exp.}\,\{-t\,(1+I)\}]/(1+I)$$

In order to get a set of curves of such a type we have plotted (using common anti-logs)

$$x=I\,[1-\text{antilog}\,\{-t\,(1+I)\}]/(1+I)$$

for different values of I; see Fig. 5. Note that three sets of curves

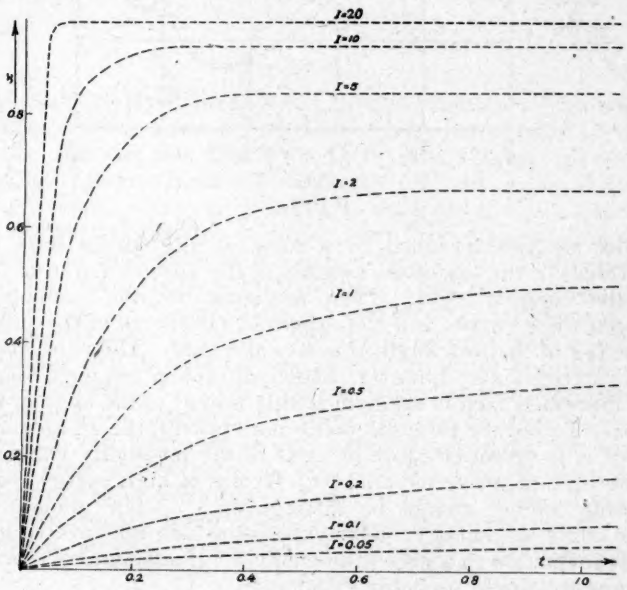

FIG. 5.

appear, the relative value of I in each set having the ratios 5 : 10 : 20. The curves are relatively crowded for very small and for very large values of I, but are more widely spaced for intermediate values. If we assume that the limit of the discrimination fraction corresponds to a fixed value of δx at the end of a flash-duration t, we shall have a relatively large value of δI for a small value of I, but the fraction will diminish and thereafter increase with steadily rising values of I, the position of the minimum being a function of t; it tends towards larger values of I, the shorter the time.

A plot of relative values of $\log \left\{ \frac{1}{\delta x} \cdot \frac{\delta I}{I} \cdot t \right\}$ against log I is shown by the curves of Fig. 6; they are derived from the last equation above.

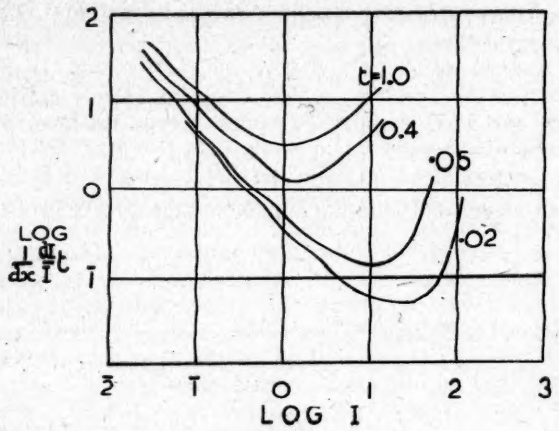

FIG. 6.

Since we have assumed δx a constant, the curves show relative values of the *log* of the product of the *discrimination fraction* and *time* against *log* I. There are some obvious resemblances between these curves and the experimental curves of the product of the *log* of *limiting angle of acuity* and *time*. The experimental acuity curves have, however, flattened minimal regions, suggesting that other factors are here setting a limit to the angular resolution. To put the essential point more briefly, the up-turn of the curves is to be expected on account of the temporary exhaustion of the light-sensitive material with flashes of high energy, so that differing stimuli cannot be distinguished. The photographic plate offers an analogy. Our experiments do *not* involve a previous adaptation to a ground-intensity I. If adaptation is secured, the up-turn would probably disappear.

For the flashes of shorter duration there is clearly no general possibility of a movement of the image over the retina which might permit of a smaller limiting angle of visual resolution. The set of curves in Fig. 5 shows, of course, nothing of the over-shooting of the steady state characteristic of discharge-frequency and electro-retinogram records, and the usual idea that the visual sensation in its early stages is a steady function of x must be abandoned. Fig. 5 may be compared with Fig. 7 which represents very roughly

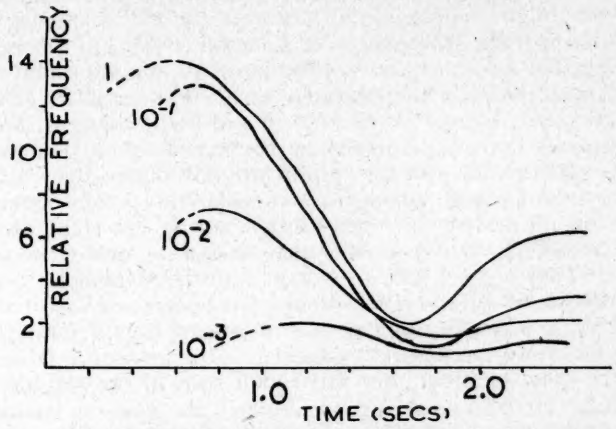

FIG. 7.

some results of Hartline (1935) on *Limulus*, which may have some relevance, even to human cone vision. Note that if pairs of curves could be drawn in Fig. 7 for a fixed ratio of two stimuli they would probably tend to crowd together both for very weak and very strong stimuli; it is thus possible to attribute the over-exposure effect either to exhaustion of the light-sensitive material or to some limitation of possible nerve-discharge frequency. The curves of Fig. 7 suggest perhaps a condenser-like action associated with the excitation of the chromophore groups in a retinal element, the ionization of some molecules and the building up of associated polarization and mechanical tension until by some means the discharge commences; it grows almost immediately to full volume as the resistance disappears in some synaptic or other valve-like connectors and thereafter decays exponentially; the subsequent (smaller) rise of the frequency to its steady level is much more reminiscent of the usual photo-chemical theory. The time scale may indicate the effects of the relief of mechanical as well as electrostatic strains. The curves of Fig. 5 can only represent the

initial variation of x due to photo-chemical action; the spontaneous discharge is not taken into account.

If indeed the above picture has any truth whatever, the initial visual photo-chemical effect would involve a very short time-scale in comparision with the very much longer periods for true photopic (much more so for scotopic) adaptation which may represent the reconstitution of chemically separated substances. If the main initial effect of the light is the electrical excitation of the ground-state molecules, the " reconstitution " term k_2x^n in *our* use of the equation might represent the return of the electrons to ground levels during the flash period, or some other leakage effect. It is possible that a re-constitution effect plays no important part in the short time intervals contemplated here. The value of k_2 would then be zero; the curves of Figs. 5 and 6 are changed, and the resemblance to the experimental curves is diminished, though some of the main features of the results are still explainable.

There is obviously room for a considerably greater amount of work on the subject of brief stimuli; we do not claim that our results are final but they offer suggestions for further investigations. They are not fully consistent with the theory put forward; for example if D.D.'s retinal image has poorer contrast than that of G.H., it would be expected that increasing intensity would produce the " over-exposure " effect at lower levels for D.D. than for the other observer, but this is not seen in the results. The difficulty of distinguishing resolution in the flash as against the after-image may be recalled. We feel as the result of these experiments that subjective observations of differing observers are most difficult to compare, owing to the different criteria which will be used even for the simpler observation tasks.

SUMMARY

These experiments aim at increasing the range of intensities beyond those for which measurements of flash visual acuity have already been made. Double-star and Foucault-grating test objects were employed, with dark-adaptation and low light-adaptation respectively. The limiting angles of resolution were found to be small (often < 1 minute) under medium intensity stimuli, and they do not suggest that eye-movements have any major effects in improving acuity. " Over-exposure " effects with high-intensity flashes are studied, and some possible connected physical and chemical processes in the retina are suggested for discussion.

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CONVERGENT STRABISMUS, MACULAR FOCI AND TOXOPLASMOSIS IN MONOZYGOTIC TWINS*†

BY

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IN an earlier paper, one of us (Granström) described a number of cases of convergent strabismus in monozygotic twins; both "concordance" and "discordance" occurred. Concordance suggests a hereditary genesis, but the latter does not exclude discordance (*i.e.*, genotypical asymmetry according to Dahlberg's theory). A monozygotic pair of twins will be described, in whom, despite pronounced concordance, an exogenous cause of the strabismus must be assumed.

As a rule, no retinal changes are present with strabismus but in exceptional cases an old focus is found in the macula of the squinting eye. This was the case in 10 instances in a series of 1,000 patients with strabismus. In a recently published paper we gave a detailed account of these 10 cases with special reference to the possible occurrence of toxoplasmosis. In six of the cases this disease could be assumed to be the probable cause of the choroid foci in the macula. In this connection the following pair of twins appears to be of interest.

The two boys were monozygotic twins, born on June 6, 1946, three weeks before term. Twin 1 weighed 2630 g. at birth and twin 2, 2800 g. The father was then 40 years old and the mother 35. Both parents were healthy and domiciled in Stockholm. They had two healthy children, a boy aged five and a girl aged seven, neither of whom showed pathological eye symptoms. The mother had had no abortions.

During the pregnancy in question the mother suffered from slight anaemia but felt well and showed no signs or symptoms of infection. She was under the supervision of an obstetrician the whole time. The pregnancy and labour were normal. The placenta was typical for monozygotic twins with a common chorion and wide anastomoses between both vascularized areas.

The children were in good condition at birth and were sent home from hospital on the 11th day. They then received breast milk only. They continued to be breast-fed until they were approximately four months old. They then had *allaitement mixte* until they were seven months old and thereafter a normal mixed diet. Both children developed satisfactorily and were very alike. The first tooth appeared in both instances at the age of six months, they could walk without support at 14 months, said a few words slightly before the age of one and talked perfectly distinctly at the age of two.

They contracted whooping cough at the age of two months. Twin 1 had it very severely and twin 2 mildly. At the age of one they were both operated on for inguinal hernia on the left side. Both had a fairly mild attack of measles at the age of 18 months. During the winter of 1948-1949, they had repeated respiratory

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tract infections which were complicated in twin 1 by otitis whereas twin 2 only showed slight symptoms on each occasion.

Twin 1 began to squint between the age of six and eight months. The squint became more pronounced during the following few months, but has remained constant since then. The parents noticed intermittent squinting in twin 2 from the age of one. In January, 1949, both children were examined at the Ophthalmological Department of Södersjukhuset and were then sent to the Sachs' Hospital for Children for further examination. Since the results of the cutaneous tests with toxoplasma antigen were positive, both children were admitted to this hospital in April, 1949, for clinical investigation. This revealed the following main points.

The children were very alike both as regards general appearance and character. They were of the same height and the colour and texture of their hair were very similar. The ears, nose, lips, eyebrows and the external parts of the eyes were very alike. Both were in good general condition and well developed physically. Intelligence tests according to the Terman-Merrill method resulted in an I.Q. of 91 in both cases. Both children had a systolic murmur, maximal between the 2nd and 3rd intercostal space near the sternum. Electro-cardiography and *x*-ray examination of the heart nevertheless revealed normal and very similar conditions in both children. There were no other demonstrable signs of disease except in the eyes. The haematological and serological tests showed the following: Twin 1 had a haemoglobin count of 85 per cent., Twin 2 86 per cent. Both belonged to the blood group combination B MN Rh (+).

The results of the ophthalmological examination were the following:

Twin 1: Testing of the vision was not possible. There was a distinct convergent strabismus of the right eye. He could focus with both eyes, but somewhat uncertainly with the right. The movements of the eyes and the pupils were normal and the media clear. Fundi: In the right macula there was a round, old chorioretinal focus, somewhat larger than the papilla, partly pigmented but mainly atrophic. As far as it was possible to ascertain, the fundi were otherwise normal. The left macula was normal. The discs were normal.

Twin 2: The findings were identical with those in his twin brother. The strabismus and choroid focus were, however, on the left side. The foci were extremely alike in both cases.

As shown in the Table the dye test according to Sabin and Feldman was positive in both children and their parents but negative in both the older siblings. Radiological examination of the head revealed no calcifications.

TABLE*

Case	Titration according to Sabin and Feldman	Intracutaneous toxoplasmin test
Twin 1	Positive (titre: 1:25)	Positive
Twin 2	Positive (titre: 1:25)	Positive
Father	Positive (titre: 1:25)	Not made
Mother ...	Positive (titre: 1:25)	Not made
Brother, 5 years	Negative	Not made
Sister, 7 years	Negative	Not made

*We wish to thank Prof. S. Gard who performed the titrations and supplied us with toxoplasma antigen.

We are thus dealing with a definitely monozygotic pair of twins, both with convergent strabismus in one eye (inverse asymmetry). In the macula of this eye there was a healed chorioretinal focus of atypical but almost identical appearance in both children. The positive serological reaction for toxoplasmosis in both children

and in the mother affords very strong evidence in favour of this disease as the cause of the macular foci and thereby—through impaired vision—indirectly of the strabismus. Despite the pronounced concordance the strabismus must in these patients be considered as exogenously conditioned.

We were able to find two reports in the literature of monozygotic twins suffering from toxoplasmosis and lesions of the eyes. One of Zuelzer's patients died at the age of one month. Post-mortem examination revealed iritis, chorioretinitis in the macula and the intraocular presence of parasites. The other twin was under observation between the age of one and seven months and suffered from chorioretinitis and microphthalmos. In Abbott and Camp's cases, both twins exhibited bilateral widespread chorioretinitis associated with retinal angiomatosis.

SUMMARY

The patients are two definitely monozygotic twins. Both exhibited convergent strabismus as well as a healed chorioretinal focus in the macula of the affected eye. Serological tests for toxoplasmosis were positive in both twins and in both their parents. Despite the pronounced concordance the strabismus must in these patients be considered as exogenously conditioned.

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THE PATTERN OF THE CORNEAL INNERVATION IN RABBITS*

BY

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As a necessary preliminary to investigations into the nature of the corneal permeability a histological study of the corneal innervation was undertaken.

Two techniques were finally chosen as being the most suitable, methylene blue and gold chloride. In general one might say that

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gold gives a better " low-power " appreciation of the whole picture, the vital stain a better " high-power " view of the detail.

In the case of methylene blue, the solution was maintained at a temperature of 37° C., and oxygen bubbled through it during the course of the staining.

The pH of the vital dye, although varied over a wide range, did not affect the final picture. Optimum results were obtained in every case between 5·6 and 7·8. The more acid the stain, however, the shorter the time required to achieve the optimum. With a pH of 6·3 ten minutes proved an adequate period. The solution was made up as described by Heller and others (1947), but better fixation was obtained, and a deviation made from Heller's method, by using 8 per cent. ammonium molybdate (in normal saline) at 0° C. overnight. The corneae were then washed vigorously in tap water for two hours, and left, again overnight, in diethylene dioxide. Finally, they were cleared in concentrated Benzyl Benzoate. A neutral mounting medium is required.

In the case of gold chloride, the method devised by Gairns (1930) was found to require no modification. Paraffin sections are more adequate than frozen if gold serials are required.

Figs. 1 and 2 give a general picture of the nerve pattern.

FIG. 1.

Superficial corneal plexus in focus. Methylene blue. ×100.

FIG. 2.

General pattern of corneal nerves. Gold chloride. ×50.

An analysis of the above pattern was made from 50 rabbits. Some 20-30 main stem branches pass into the substantia propria deep to the dark limbal epithelium. These large nerve bundles, as is well known, lose their myelin sheaths within the first millimetre. This we confirmed.

Branching dichotomously the nerve fibres form networks at three levels, one within the substantia propria, occupying its whole breadth, one under Bowman's membrane, and one within the epithelium. The fibres tend to become progressively finer, but many fine solitary fibres are also present in the stroma (Fig, 3). Skeins with radiating free endings and loops occur at all levels, and can be seen in Fig. 1. No specialized end organs were found.

None of the main stem branches " anastomose," although fibres derived from the same parent main stem frequently do so. Daughter branches from two or more main stem bundles, although not " anastomosing," constantly overlap.

With gold the " anastomoses " and dichotomous branching are more readily seen. The *boutons de passage,* however, are overlaid and masked by the heavy metal.

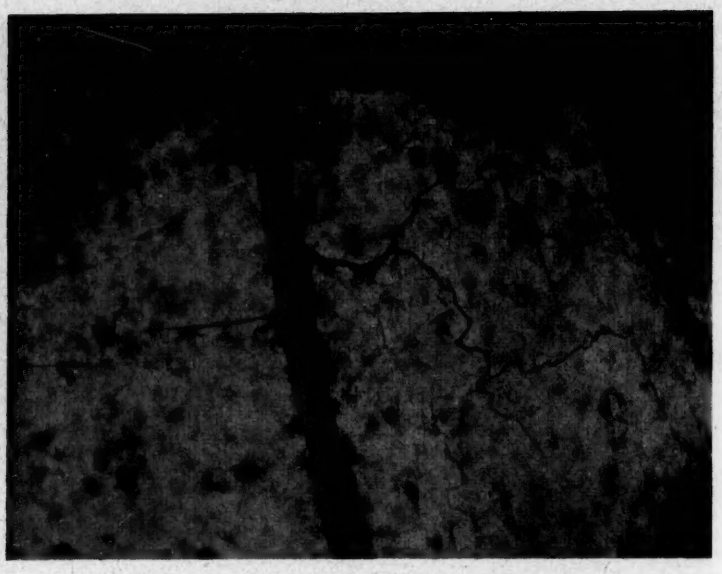

FIG. 3.

Fine free ending in corneal stroma. Gold chloride. ×350.

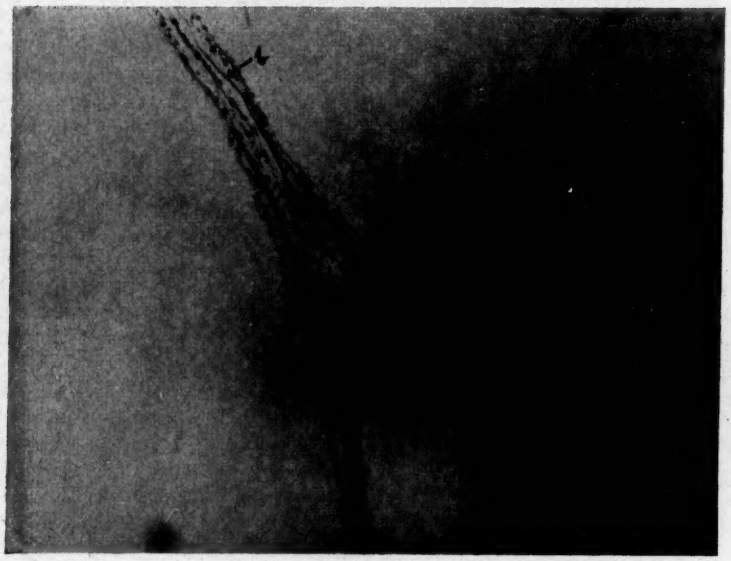

FIG. 4.

Two types of fibres in corneal nerve bundle. *a*, beaded. *b*, non-beaded. Methylene blue. ×600.

FIG. 5.
Intra-epithelial plexus. Gold chloride. ×770.

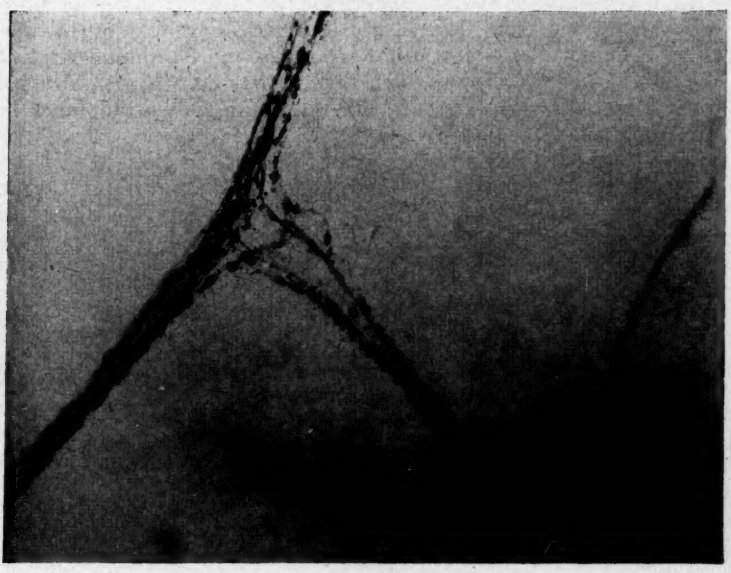

FIG. 6A.
Photomicrograph before fixation. Vital stain.

FIG. 6B.

Photomicrograph after fixation. Vital stain.

In the vitally stained preparations two distinct types of fibre were found to exist in the nerve bundles (Fig. 4). In one (Fig. 4, fibre a) the *boutons de passage* are more pronounced, but the linking nerve processes finer, than in the other (Fig. 4, fibre b). Such a marked morphological difference suggests a difference in function.

The markedly beaded type of fibre—which occurs in varying sizes—is of course typical of the denditic ramifications of the cutaneous sensory nerves. The other we have seen in the skin, and in the iris, as well as in the cornea. In the skin they are especially prominent in the vicinity of blood vessels. These coarse fibres may well, then, prove to be autonomic.

Finally, the nature of the superficial so-called " free " nerve endings in the epithelium was observed (Fig. 5).

It would appear that the pain " end-buttons "—as they are sensory may not the phrase " *boutons premiers* " be coined?—do not end within the epithelial cells, but on and between them. Passing up in many instances to the surface, they form long arcades immediately below the outermost layer of the stratified squamous epithelium. Morphologically one cannot exclude the possibility that some of these endings may belong to autonomic axis-cylinders.

It was found that photo-micrography before fixation of the vitally stained nerves revealed details lost completely in the process of fixation. This may explain why the two types of nerve fibre have not previously been described (Figs. 6 A and 6 B).

SUMMARY

1. The pattern of the corneal innervation is shown in methylene blue and gold preparations.
2. Two types of nerve fibre are described, occurring in the multifibre nerve bundles: a large beaded one with a fine dendritic link, and a second where the beads are masked.
3. The possibility that the second of these fibres is autonomic is cited.
4. The boutons of the intra-epithelial plexus are clearly demonstrated. They do not end within the epithelial cells.
5. Photo-micrography of vitally stained specimens before fixation is essential.

The author's thanks are due to the trustees of the King's College Research Fund for a grant received for this work, and to the Director of Photography, King's College, for the gold chloride photo-micrography.

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STENOSIS OF THE LOWER CANALICULUS*

BY

O. GAYER MORGAN

London

THE literature on treatment of stenosis of the lower canaliculus is not very extensive and this is my excuse for recording the few cases which I have had to deal with over a period of a good many years. An impervious fibrous stricture after trauma seemed to be a particularly troublesome condition, but I have had this small series of cases in which, by utilizing the upper canaliculus, a functional success has been achieved.

The first case was that of a girl who was injured in a ski-ing accident, the point of the ski penetrating the orbit on the inner aspect. It went through the lower lid obliterating the lower punctum and about half the lower canaliculus. I saw her some months after the accident when the wound had healed with only slight deformity. After testing the passage to the nose *via* the upper punctum and finding it clear, I slit the upper canaliculus in its

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whole length as far down as possible and inserted a small wool wick into the lower open end. This was removed after three days and the opening has remained patent, can be entered by the lacrimal nozzle and the passage is clear to the nose. Epiphora which was extremely disconcerting has practically ceased and she had been quite comfortable for 2½ years when I last saw her.

Four other cases have been treated in this way: one being traumatic, the patient having run into the sharp corner of a cupboard in the black-out, and three being strictures near the ampulla presumably from infection as there was no history of any injury. Of these, three were successful and one of the infected ones a failure, but in none of the three successful ones can I find the opening with a probe or dilator though fluorescein passes into the nose and there is no complaint of epiphora. As two of the successful ones have been comfortable for over 6 years, there must be a well lined though minute opening which shows no sign of closing.

A sixth case was that of a boy who was attacked by a dog and bitten or scratched over the inner aspect of the left eye and nose. There was considerable damage to the lacrimal bone and the lower canaliculus was blocked. Three years after the injury pus could be expressed from the sac *via* the upper punctum and a dacryocystorhinostomy was performed with some difficulty owing to bony thickening. Before suturing the nasal and lacrimal flaps together a probe was passed up into the fundus of the sac and then into the lower canaliculus where it could be seen between the lower punctum and the medial canthus bulging the lower lid. An incision was made on to the point and this was pushed through the opening which was made on the inner aspect as much as possible. The probe was then bent over and strapped to the skin of the lower lid. The excess of probe still in the sac was nipped off with wire cutters and the dacryocystorhinostomy completed. The probe was kept in for a week and then removed. A small opening was clearly visible and this was dilated every few days and the passage syringed to the nose. Three years have passed and the condition is quite satisfactory, and the opening can still be found quite easily.

After this success the other unsuccessful case was recalled for further operation. The sac was exposed and a probe passed, and the same operation performed. This has also been successful.

In conclusion it would seem to be worth while first trying to utilize the non-functioning upper canaliculus. I think that, if a fine short probe were inserted through the lower end of the slit canaliculus into the sac, bent over and kept in position for a few days, there would remain an opening which was identifiable.

I have an uneasy feeling that my successful cases in which no opening can be found will one day come back with epiphora and will need the more complicated approach to cure this disability.

THERAPEUTIC CONTACT-LENSES FROM PLASTIC *†

BY

ISTVAN DE GYÖRFFY

Budapest

THERE has been a great improvement in ophthalmologic prostheses during the last twenty years. Artificial eyes, contact-lenses, and recently ocular implants have become so numerous that they have begun to represent a special branch of ophthalmology. In this publication I wish to speak about prostheses in the form of contact-lenses which are made from plastic and are used successfully for therapeutic purposes in modern ophthalmology.

The first to write about the therapeutic use of contact-lenses were Galezowski (1882) and Mules (1894) who applied gelatine shells impregnated with drugs to the eye in order to protect it from infection, or to cure corneal abscess.

The ordinary contact-lens was first used therapeutically by Weihmann (1923) for the treatment without bandage of corneal ulcer and for diseases of the corneal epithelium. No drugs were used and the essential form of treatment was protection. Huber (1934) used a contact-lens containing ointment in the treatment of various conditions. The advantage of this method was obvious, and others made use of it in the application of different drugs. The therapeutic use of contact-lenses has become especially important since the introduction of sulphonamides and penicillin, as no other method can bring the diseased cornea into such prolonged and close a contact with the drug. It is especially valuable to try this method when the disease is so deep-set or so severe that treatment consisting of the instillation of solutions or application of ointment does not prove efficacious. In order to obtain prolonged local effect of vitamins and anti-histamin drugs this method can also be recommended.

Contact-lenses also prove effective in preventing desiccation or erosion of the cornea. Entropion and trichiasis may be treated in this way until surgical treatment is undertaken, or in cases when an operation is contra-indicated. Contact-lenses are also useful in cases of keratitis *e lagophthalmo*, and the necessary correction may be ground on to the lens. Contact-lenses can be used in combination with surgical treatment. In the literature Rosengren (1930) reports that he used them with good effect to fix the disc after keratoplasty and Wright (1932) mentions a similar case. They also used contact-lenses after operations for detachment of

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† From the Second University Eye Clinic, Budapest, Hungary.

the retina. Klein (1935) has used them in order to ensure transparency of the cornea in ophthalmoscopy. Aust (1929) uses them in cases of high astigmatism in order to clarify the view of the fundus. Contact-lenses may prove useful after Blaskovic's operation for ptosis instead of the protective glass-cup dressing, and assist in preventing erosions caused by sutures placed in the upper lid. Muller-Welt (1926) devised a special contact-lens for the treatment of ptosis. This shell has a horizontal strip in its upper part to support the upper eyelid.

Knapp (1925) recommends contact-lenses filled with ointment for cases in which the cornea is tattooed with chloride of gold, in order to avoid the corresponding portion of the palpebral conjunctiva being tinted, and Mayerbach (1926) reports a case in which he used Muller's contact-lens for the protection of pulsating descemetocele. With all these methods ordinary or slightly modified lenses were used which prevented access of air to the cornea.

Another group of therapeutic lenses are the ocular shells. These are contact-lenses which have openings in front of the cornea, so that it is possible to have access to the eyeball, the shells having to remain in the eye sometimes for weeks without being removed. Hanke (1916) and Majewski (1916) as well as Illig (1917) and Carsten (1917) were the first to advocate their use to prevent the development of symblepharon, after burns or other injuries. They are useful after recent burns, as the part behind the shell can be well flushed through the opening in front of the cornea, and the instilled drug can reach the whole surface of the bulbar and tarsal conjunctiva. When cicatrization has set in, the shell regulates the shape of the conjunctival sac and prevents the development of adhesions. The perforated shells are very useful for stopping recurrence of smaller symblepharons and ankyloblepharons after severing scars or strands. A shell of the appropriate size and shape is inserted and new adhesions can be prevented. We used this method very successfully when scars had to be removed which prevented the wearing of artificial eyes and tinted lenses, and the complicated operation of transplanting mucous membranes was not necessary in less severe cases. In all these cases plastic shells were used in preference only to glass, porcelain or metal. In cases requiring ordinary contact-lenses the shell can be made from sheet plastic 0·2-0·3 mm. thin, so as to be no more than a membrane between the eyeball and the lid. Thus it is extremely elastic and pliable, and even when the eyeball is not spherical the shell tends to take its shape and is comfortable to wear. If necessary the corneal part can have a correction ground on to it. The material itself is indifferent to the lacrimal fluid, and it can be perfectly cleaned and sterilized in a solution of 1 per cent.

mercuric oxycyanate. The perforated shells (Fig. 1) are made from thicker (1·0-1·5 mm.) material. This is better for prevention of symblepharon. We generally make a corneal opening of 10-12 mm. Through this opening the bulbar conjunctiva can be well irrigated and the absorption of instilled drops is more complete. By reason of the extremely easy moulding properties of acrylics the shells can be rapidly adjusted.

In connection with plastic lenses I should like to mention a new moulding-shell (Fig. 2) which I have found useful. Many authors

FIG. 1.—Ocular shells.

FIG. 2.—Moulding shell.

have recommended moulding-shells—Csapody (1929), Prister (1933), Obrig (1938), Maisler (1939), etc. All these shells are good, but some prefer one type and others another. The characteristic of my shell is that it is a larger contact-lens made from plastic, having a small handle attached to the centre of its corneal part. This handle has a central hole to which a record syringe can be fixed. The inner side of the plastic shell is roughened to ensure better adhesion of the moulding material. The moulding process is carried out by inserting the shell into the anaesthetized eye of the recumbent patient, and injecting moulding material from the syringe under the shell through the opening in the handle. It is an advantage that the psychic irritation which the patient feels when the lens is inserted is avoided, as well as the resulting blepharospasm. The patient lies on his back, and is told to fix a sign on the ceiling, and, as the shell is in his eye, he does not notice when it is being filled with moulding material. The syringe is placed upon the handle, the shell is slightly raised from the eyeball, 2-4 cc. of liquid moulding material are instilled, the shell is slightly pressed back upon the eye, and the syringe is immediately removed. As the moulding material stiffens very quickly, it cannot flow back through the opening in the handle, and if the patient were to move his eye the whole shell would move with it, so that the mould could not get out of shape. Removal is carried out in the usual way. This method requires a certain amount of practice, as no air should remain under the shell, but after a few trials no difficulty is found.

Finally, I should like to mention, as advantages of the lenses made from plastic, that being unbreakable they do not require frequent replacement, and that being simpler to make than the glass variety, they are cheaper.

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SELF-INFLICTED CONJUNCTIVITIS*

BY

M. J. ROPER-HALL

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FROM February to June, 1949, in the Suez Canal Zone, 22 cases of self-inflicted conjunctivitis were seen among Mauritian troops, and 1 case in a British soldier under detention.

History. The history of these patients usually showed that they were temperamentally unsuited to the army. Their attitude on arrival in the department, the clinical appearance with negative pathological findings, and the course of the condition, left no doubt that these inflammations were self-inflicted. This was proved by the investigations outlined later in this article.

At the time of greatest incidence there was no epidemic of conjunctivitis among British troops or natives, and during the whole period only one case of a true conjunctivitis occurred in Mauritians seen in the department.

Clinical Picture. The cases presented the clinical picture of a patient crouched in a chair, nursing his bandaged eye and groaning in apparent distress. When an attempt was made to examine the affected eye, the groaning increased in intensity, with a marked tendency on the part of the patient to resist or avoid examination.

There was oedema of the lids with a serous or sero-purulent discharge. All except two cases showed severe chemosis in one or both fornices of one eye only, with relatively little affection of the bulbar conjunctiva. The left eye was affected slightly more often than the right. Two cases showed a membranous reaction in the lower fornix.

The cornea was clear on first examination, except in one case which showed a generalized corneal haze with a more dense opacity at the limbus above. The diagnosis was made clear in two other cases which later developed corneal abrasions. A subconjunctival haemorrhage was present in one case. In only one case was any foreign matter found; a small white fleck in the upper fornix, the nature of which was not discovered.

Clinical Investigation. Stained smears of the discharge showed only necrotic neutrophil polymorphs and epithelial cells. Routine culture showed no growth after 48 hours except in one case with a scanty growth of Strep. Viridans. Histological examination of one of the membranes showed fibrin with neutrophil polymorphs and lymphocytes.

Treatment. At first these cases were regarded as genuine, and treated as acute bacterial conjunctivitis. The eye usually improved

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rapidly, and then showed repeated exacerbations and deterioration. After this indulgent treatment there was a marked increase of incidence in March and April (16 cases). As a deterrent measure intra-muscular injections of 6 cc. of boiled milk were given on alternate days; this usually resulted in a rapid improvement.

It was found, however, that cases so treated returned after a short interval, so it was decided to return all cases to their units without treatment, but with the recommendation that suitable unit discipline be carried out. This led to a sharp reduction in the incidence in this form of malingering and no cases occurred in May. Since then there have been only sporadic cases among fresh drafts arriving in this zone.

Further Investigation. It was felt that confirmation of our findings should be obtained by visiting units which had provided most of the cases. During a short interview it was possible to obtain a great deal of useful information. Most of the patients who had shown this condition had recovered both physically and mentally, and were now doing useful work. They were interviewed, with the guarantee that no disciplinary action would be taken, as this was part of a medical investigation to discover the method of production of the conjunctivitis. Having this assurance the men spoke freely.

It was found that the popular method of production in Mauritius was by the seeds of the Chillie plant which grows plentifully there. These seeds are either red or green, and were usually placed in the upper fornix for 24 hours, after which they were removed and the patient would report sick. A few patients had brought the seeds with them, but the majority had to look for some other method as the plant is not grown here. In one unit cordite was removed from cartridges and distributed fairly widely in the unit concerned and other units. The flakes of cordite were used in a manner similar to the use of the seeds. Another method was the application of atebrin tablets which are easily obtainable. In the course of the interview methods of production of many non-ocular conditions were also explained.

A discovery which was surprising to us was that these patients once having been exposed did not attempt other means of evading duties, but in most cases settled down to give useful service.

It was felt to be worth recording this series of cases because it reflects the speed with which the men realised that this condition offered an easy opportunity of spending a few days of relative holiday in hospital—an opportunity which was taken with increasing frequency. When a firm line of action was adopted, realisation again spread rapidly, so that the condition now hardly ever occurs.

ORGANIZATION OF A PHOTOGRAPHIC DEPARTMENT*

BY

GYULA P. HALBERG

Instituto Oftalmologico Pedro Lagleyze, Buenos Aires

ON June 1, 1948, Professor Jorge L. Malbran entrusted me with the task of organizing a photographic department for the Instituto Oftalmologico Pedro Lagleyze. Some of the foundations had already been laid and, therefore, my scope was somewhat limited.

Provision had to be made for the following types of work :—

(1) Photography of the optic fundus.

(2) Photography of external conditions of the eye (including whole face or larger areas).

(3) Recording of small specimens.

(4) Document copy work, etc.

At the outset, photography in both colour and monochrome was visualised, though it was realised that infra-red photography could not be undertaken on account of the complete lack of suitable plates or film in South America.

Equipment.—We employ miniature camera technique, having two Leicas (III B and C). One is kept loaded with monochromatic stock and the other with colour; thus an interchange can be effected quickly. The range of lenses at our disposal includes the 5 cm. Elmar and Summitar, the 9 cm. Elmar, and 13·5 cm. Hektor. In addition the Leitz " Nooky " close-focusing attachment and the reflex-housing are available.

To provide a working table we have replaced the usual slit-lamp table-top by a larger one (45 x 100 cm.). This enables us to undertake photography of the anterior segment or of the whole face with the same set-up. The patient is comfortably fixed with the conventional head-rest. The general disposition of apparatus is indicated in Figs. 1 and 2.

Illumination.—For much of the work we are able to use two ordinary 500-watt Nitra-type bulbs mounted in reflectors and adjustable supports. During focusing the lamps are switched in series, a foot-switch enabling them to be brought up to full brilliance when required (Halberg, *Argentine Soc. Ophth.*, September, 1948). The usual photo-electric meters are used for estimating exposure.

A short time ago we obtained an electronic discharge tube outfit (electronic flash). This has an emission of about 40,000,000 candle-power per flash, the duration being about 1/7,000th of a

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FIG. 1.

Leica camera with reflex-housing and long focus lens, on Zeiss optical support. Note also electronic flash tube equipment.

FIG. 2.

Leica camera fitted with "Nooky" near-focusing attachment. Note also power-pack for electronic flash tube.

second. This intense light is constant and facilitates the standardization of exposures; an additional advantage is the great depth of focus which is obtained by virtue of the small apertures employed. The ordinary lamps mentioned above are used for setting up and focusing. It should be mentioned that the light emitted by the electronic flash tube is predominantly blue and, therefore, daylight colour film is the one of choice to use with this light unless correction filters are to be considered.

To obviate errors and reflections, the walls and furniture of the studios are painted a dark grey and the photographic staff are provided with black coats.

Fundus Photography.—For photography of the fundus we use the Zeiss-Nordenson camera. It is the new model fitted with a Nitra lamp, though use of the electronic flash tube is contemplated in this connection.

We have modified the camera slightly in that a Leica body is used for transporting the film. This has necessitated cutting off about 30 mm. of the main tube of the Nordenson camera and inserting an intermediate plaque (Figs. 3 and 4). It will be obvious that the tube of the inspection eyepiece has to be similarly modified in order that it may remain par-focal with the film plane.

The remainder of the equipment is standard, and the Wessely fixation device is used with good effect. The only other modification is that the hand-control has been replaced by a foot-switch.

Film stock of the usual types may be used, but we favour the fine-grain materials, and for colour work we have found Kodachrome A and Anscocolor Tungsten both yield good results.

To avoid technical errors and to preserve a high standard of work, it is important to standardize both materials and processing. It is also useful to photograph serial numbers or other identification marks on the first frame of each film used.

Filing and Processing.—Films are stored in strips of six pictures which are contained in numbered transparent envelopes; these are held under slight pressure to obviate curl.

A modern photographic laboratory is at our disposal for the processing of films and production of enlargements. Since this side of the work is strictly conventional, details are not considered relevant.

Administration.—The medical staff is free to use the facilities of the photographic department, and all patients are sent with a "Request for Photography". This is in the form of a card on which appears all the necessary information, which is later transcribed into a day-book. In this are recorded such details as

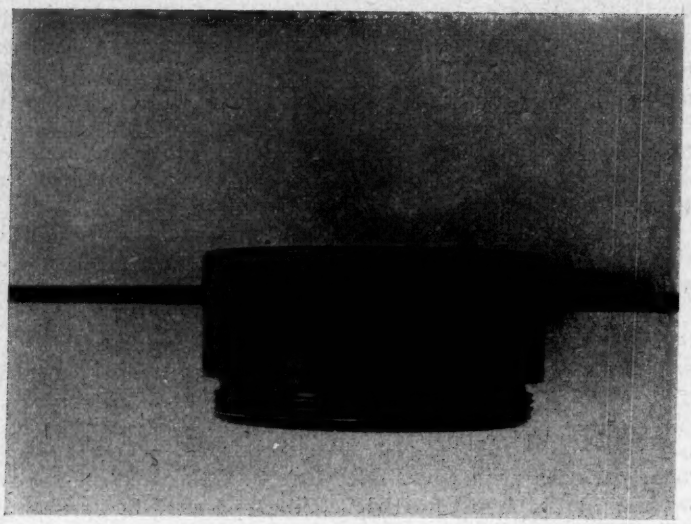

FIG. 3.

Intermediate plaque (side view) for fitting Leica body to Zeiss-Nordenson camera.

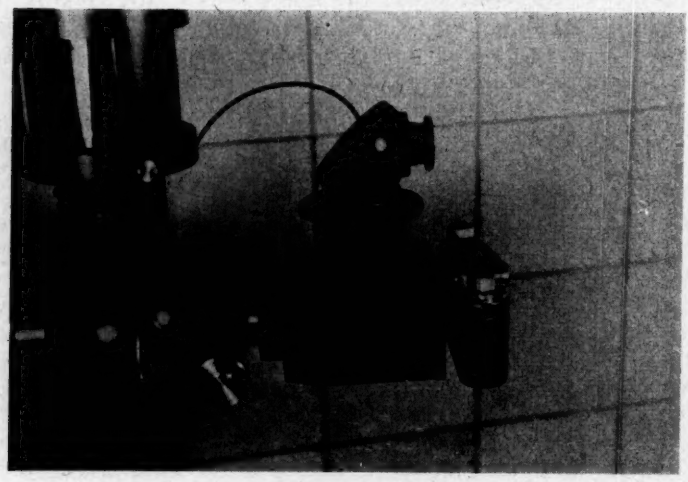

FIG. 4.

Leica body in position near film plane of Zeiss-Nordenson camera. Note the extended tube of the observing eye-piece.

date, name, diagnosis, physician, type of record and registration number. In the near future it is hoped to establish a cross-index between patients' names and disease processes.

SUMMARY

The establishment of a photographic department within an Ophthalmic Institute in South America is described. Particular mention is made of electronic flash as a source of illumination, and reference is made to some modifications of the Zeiss-Nordenson fundus camera.

BOOK NOTICE

Biomicroscopy of the Eye (Vols. 1 and 2). By M. L. BERLINER, M.D. 1512 pages, 1233 illustrations (503 in colour). Cassell and Co., London, 1949. Price, £18.

Berliner's text-book on the biomicroscopy of the eye must undoubtedly rank as one of the most important books in American ophthalmological literature. The first volume appeared some years ago: it has now been revised and brought up to date and is published with the second, the two together comprising a detailed and authoritative treatise on the biomicroscopy of the eye which stands comparison only with the Atlas of Vogt. Biomicroscopy is viewed in its widest sense and includes not only the examination of the eye with the slit-lamp (called the biomicroscope, a term with more dignity than the usual direct translation of Spaltelampe into English) but also such techniques as gonioscopy and the examination of the posterior region of the vitreous and the central area of the fundus with a —50 D. lens. The development of these clinical methods is detailed, their optical principles and clinical application discussed in detail, and the biomicroscopical appearances of each tissue in the eye from lid-margins to retina described both in the normal state and in the multitude of pathological conditions from which they may suffer.

Berliner has accomplished his cousiderable task with undoubted credit; both the written matter, which is detailed, authoritative and very readable, and the numerous illustrations, both coloured and uncoloured, which form so important a part of a book of this kind, are excellent. The chapter on gonioscopy (of 72 pages) has been written by Dr. H. Saul Sugar and is equally good. Each chapter is up-to-date, the biomicroscopic appearances of aqueous veins, for example, or the appearances of macular holes and oedemas receiving the same attention as the clinical appearances of the cornea or lens which have become established in knowledge for more than a generation. Not the least useful parts of the book are the exhaustive

bibliography of 686 references and the very useful index appended to each volume. The ophthalmic world is deeply in Dr. Berliner's debt, and no ophthalmological library will be complete without this volume.

In the production as a whole the publisher must also receive much credit. The book is luxuriously produced, well printed, and the multitude of illustrations are outstanding in their artistry and clarity.

OBITUARIES

REGINALD ERNEST BICKERTON, D.S.O., T.D., M.B., Ch.B.

R. E. BICKERTON, whose death at the age of 79 was recently announced, had been for 42 years Ophthalmic Surgeon to the Dreadnought Seamen's Hospital, Greenwich, and was Consulting Ophthalmic Surgeon to the Evelina Hospital for Sick Children, and to the Royal Waterloo Hospital for Women and Children. He did valuable work for St. Dunstan's and was chairman and visiting Ophthalmic Surgeon to the Royal School for the Blind, Leatherhead. He was Hon. Surgeon to the King, 1927-32.

In the 1914-18 war he performed distinguished service as an ophthalmic surgeon mainly in the Mediterranean theatre, being twice mentioned in despatches and winning the D.S.O.

Bickerton was loved and respected by all who knew him. He had a remarkable presence, urbane, kindly, and always completely unruffled however trying the circumstances. He approached ophthalmic problems in a leisurely and contemplative fashion, never forgetting the personality of his patients. He would start his out-patients at the Dreadnought in the late afternoon, and the work would go steadily on until past midnight. It was in vain that officious residents endeavoured to clear away some of the old patients. They simply refused to budge until they had seen the Great Man. Bickerton had an unrivalled memory for names and faces; and as each patient entered, would greet him as a friend, asking in detail about various members of the family who had been seen at previous visits. The writer well remembers how the Greenwich patients would bring their children and discuss what careers they should take up, receiving shrewd advice from the ophthalmic surgeon. When eventually the discussion came round to ophthalmic matters, Bickerton's advice was always practical, concise and sound, well worth the long wait for the patient.

In ophthalmology, Bickertons's interests leaned to the medical side; but his cataract and glaucoma operations were pretty to watch and very successful.

He will be greatly missed for his kindly personality and his fund of inimitable anecdotes.

L.H.S.

MARK CLAYSON GARDNER, M.C.

THE news that Mark Gardner died in November, 1949, will be deeply regretted by his friends all over the world. For many years he was one of the foremost ophthalmologists in Melbourne, where he was particularly respected for his wise clinical judgements, and for the generosity with which he encouraged his junior colleagues. Having graduated M.B. at Melbourne in 1908, he subsequently became M.D., and also acquired the D.O., as well as the Fellowship of the Australasian College of Surgeons. He served in the 1912 Balkan war, during which he was working for many months with Mr. Page (now Sir Max Page, D.S.O.), a distinguished surgeon of St. Thomas's Hospital.

From 1914-19 Mark Gardner performed varied and valuable tasks with the R.A.M.C., and he received the Military Cross in 1917. Then in 1919 he became House Surgeon at Moorfields Eye Hospital, as the immediate junior of William Simpson, who now practises in Wellington, New Zealand. After returning to his home city, Mark rapidly gained a prominent position in ophthalmology. He was elected to the staff of the Victorian Eye and Ear Hospital, the Children's Hospital, and other institutions. In 1935 he presided over the Victorian Medico-Legal Society, which he had himself founded four years previously. He also became a member of the Council of Trinity College, Melbourne, and was chosen Honorary Treasurer of the Melbourne Medical Association. Throughout the second world war he did excellent work as Consultant Ophthalmologist at the Heidelberg Military Hospital, Victoria.

Although he had undergone a serious operation towards the end of September, 1949, Mark took a lively interest in the Annual Congress of the Australian Ophthalmological Society held at Melbourne last October. He looked frail, but nevertheless cracked many a joke, and was not in the least anxious to dwell on his own troubles. The writer of these notes can never forget Mark Gardner's humour, pluck, and width of interest, and the immense personal kindness which enabled him to put a guest immediately at ease. The years which he spent in the Old World brought him new friendships, new interests, and a profound respect for tradition, but nothing ever damped his zest for the spacious country of his origin. He was above all else an Australian, who played a worthy part in the immense contribution of Australia to medicine and surgery. It is good to hear that Richard Gardner, now a junior law student at Melbourne University, rivalled his late father's triumphs at school. With him, with Miss Gardner, with the younger sons, and above all with Mrs. Gardner, the readers of this Journal will assuredly sympathize.

J. H. D.

RICHARD SEEFELDER

PROF. R. SEEFELDER, who died on October 12, 1949, was born in Bavaria in 1875, graduated at Munich and started his early medical career as a regular army medical officer in the Saxon army. In 1904 he was seconded to the University Eye Hospital, Leipzig, then under Sattler. His appointment to the chair of Ophthalmology at Innsbruck University, as successor to Meller, followed his discharge from the army after the first world war in 1919. He stayed at Innsbruck for the rest of his life.

In this country, as indeed almost everywhere in the ophthalmological world, Seefelder was best known as the co-author and editor with Bach of the "Atlas of the Development of the Human Eye". Publishod in 1911, this monumental and most beautifully illustrated work became a classic. In later years he covered the same field, together with that of developmental abnormalities, in two large chapters of Brückner-Schieck's "Kurzes Handbuch der Ophthalmologie" (1931). But his interests were by no means confined to this semi-academic approach to ophthalmology. In his early days at Leipzig he made a valuable contribution to the aetiology and clinical study of jequirity ophthalmia. In the late '20s and early '30s of this century he was amongst the first to establish recognition for Boeck's sarcoidosis as a separate entity in the mass of aetiologically ill-defined chronic affections of the outer and inner eye which, so long as they were not definitely syphilitic, were all somewhat summarily attributed to tuberculosis. At congressional meetings he was a clear, refreshingly uncomplicated, and straightforward speaker.

P. L. K.

NOTES

Lectures

A COURSE of Three Public Lectures entitled "Visual Physiology" will be given by Dr. L. C. Thomson, Ph.D., M.B., B.S., Vision Research Unit, Medical Research Council, Institute of Ophthalmology, on Tuesdays at 5-15 p.m., at the Physiology Theatre, Gower Street, W.C.1.

Syllabus:—February 7, What *are* the problems?; February 14, Colour Vision and the Brightness Mechanism; February 21, Foveal Tritanopia.

* * * *

Erratum

B. J. O., Vol. XXXIV, January, 1950. P. 38, para. 2, line 13, for: "The capillary canula, bent at an angle of about 120°, is drawn from a and cut to approximate to the required size", read "The capillary is compared under the microscope with the central vessels and cut to approximate to the required size".